NOCDURNA®
Desmopressin Orally Disintegrating Tablet (Melt)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

January 12, 2015

NOCDURNA® Introduction Desmopressin Orally DisintegratingTablet (Melt)

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Vice President, US Regulatory Affairs,
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Proposed Indication for NOCDURNA

NOCDURNA is indicated for treatment of nocturia due to nocturnal polyuria, in adults who awaken two or more times each night to void.

Prior to treatment with NOCDURNA, lifestyle changes and other treatable medical causes of nocturia should be addressed.

Study Population Appropriate for Proposed Indication

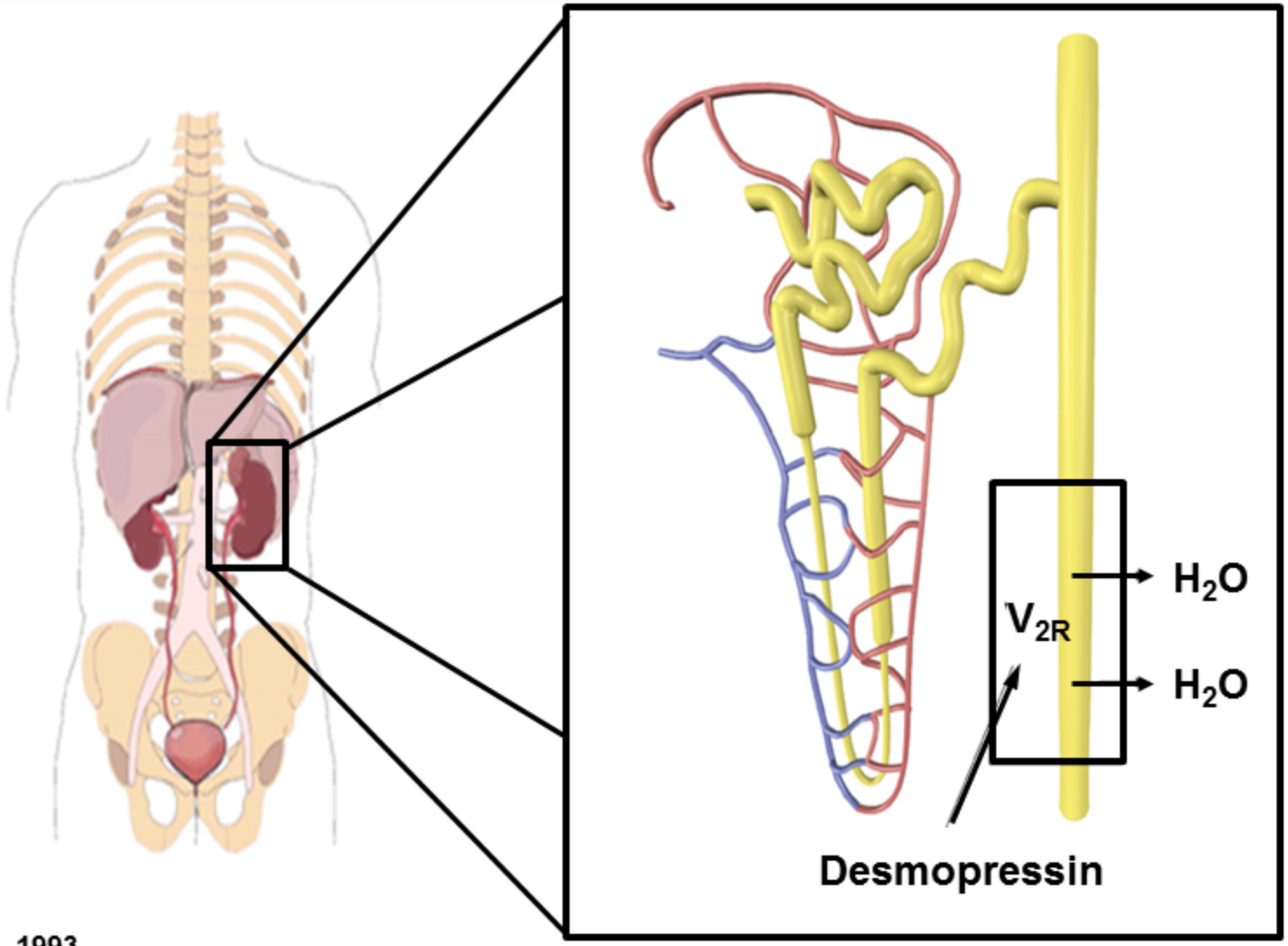
- Indication accurately reflects
  - Population studied
  - Unmet medical need
  - Mechanism of action of active ingredient

Nocturia is Awakening at Night to Void

- Nocturia definition: awakening ≥ 1 time to void at night[1]
- Threshold for clinical relevance: awakening ≥ 2 times to void[2,3]
  - Can significantly impact sleep, daily functioning and overall health and well-being[4,5]

1. Van Kerrebroeck, et al., 2002
2. Tikkinen et al, 2010
3. Yu JH et al., 2006
4. Asplund and Aberg, 1996
5. Van Kerrebroeck, et al., 2014

Desmopressin Acts as a Vasopressin Agonist to Decrease Urine Output

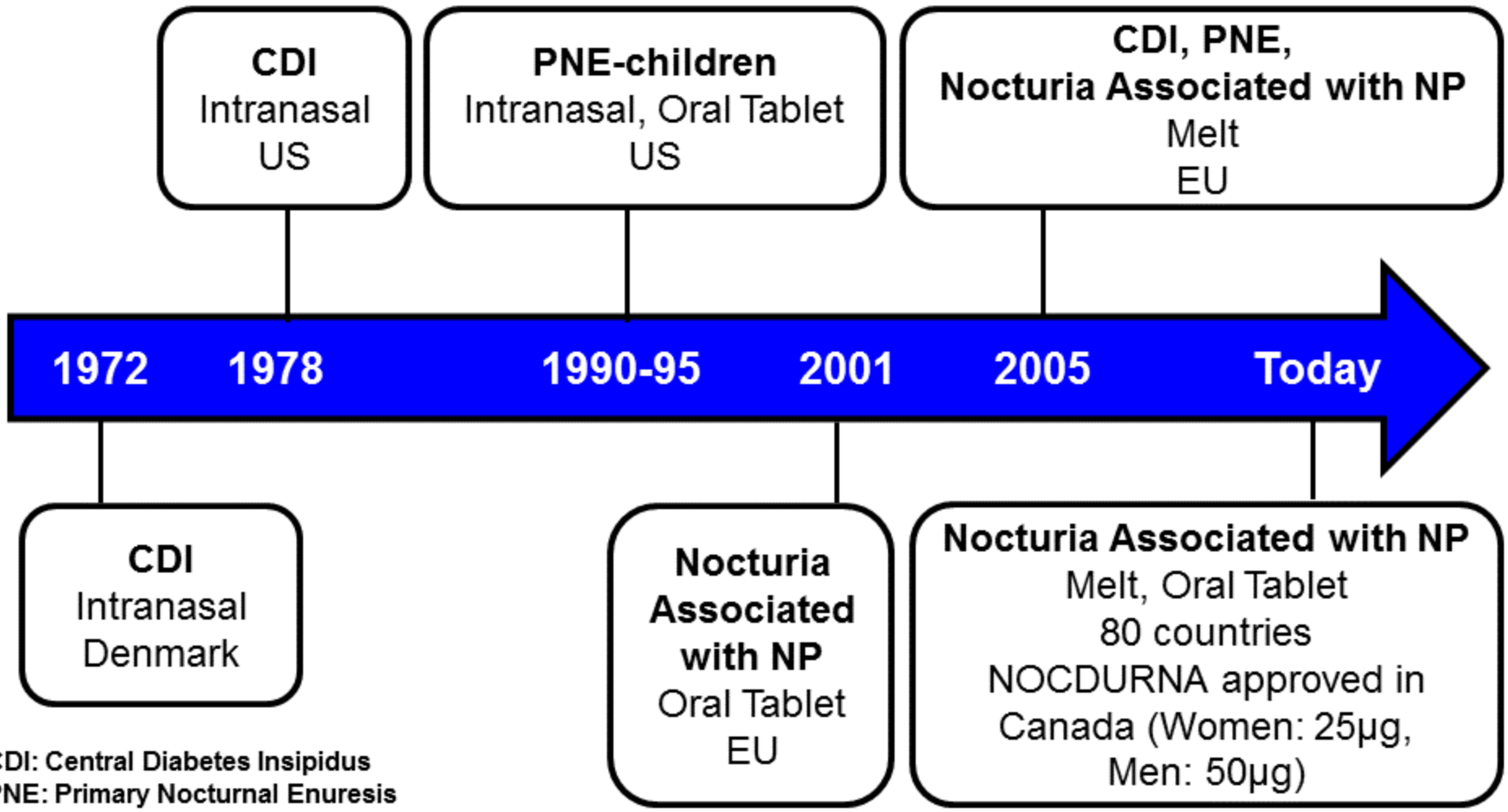


Nielsen et al., 1993

Nocturia Clinical Development Program

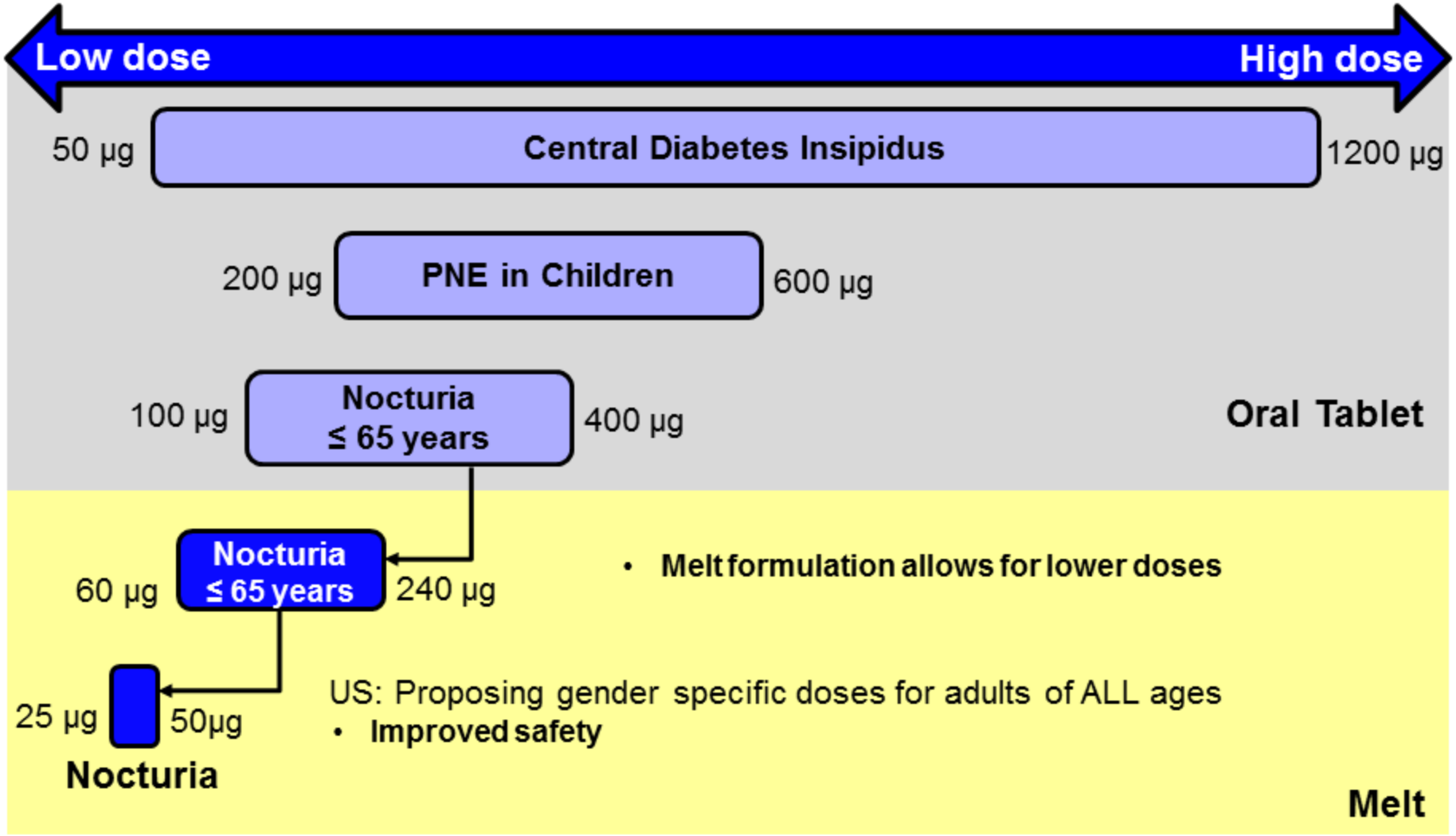
- 3 NOCTUPUS pivotal, global trials and 2 extension trials with tablets
- U.S. NOCDURNA Program with melt
  - Initial pivotal study CS29
  - 1 extension trial to evaluate long-term safety (CS31)
  - Confirmatory pivotal studies CS40 (Women) and CS41 (Men) under Special Protocol Assessment (SPA)

Desmopressin has Been Approved in Various Indications for Decades



CDI: Central Diabetes Insipidus
PNE: Primary Nocturnal Enuresis
NP: Nocturnal Polyuria

Desmopressin History Leading to Gender-Specific Low Doses for Nocturia



PNE: Primary Nocturnal Enuresis

NOCDURNA Formulated for Optimal PD Profile for Nocturia due to NP

- Anti-diuretic effect occurs 15-30 minutes after administration
- Reaches maximum effect in 1-2 hours
- Duration of action
  - Dose-dependent
  - ~5 hours
  - Rapid anti-diuretic effect at nighttime, significantly reduced by morning

Agenda

Nocturia due to Nocturnal Polyuria	**Eric Rovner, MD** Professor of Urology Medical University of South Carolina
Efficacy Results	**JensPeter Norgaard, MD, DMSc** Professor of Urology, Global Scientific Affairs, Urology, Ferring Pharmaceuticals
Additional Clinical Relevance/Sleep	**Donald Bliwise, PhD** Professor of Neurology, Emory University School of Medicine, Atlanta, GA
Patient Reported Outcomes/QoL	**Raymond Rosen, PhD** Chief Scientist New England Research Institutes, Inc.
Safety	**Vladimir Yankov, MD** Vice President, Reproductive Health & Urology Ferring Pharmaceuticals
Hyponatremia	**Joseph Verbalis, MD** Professor and Chief Division of Endocrinology and Metabolism, Georgetown University
Benefit Risk/Conclusion	**Eric Rovner, MD**

Additional Experts

Per Cantor, MD, PhD (Moderator)	Senior Vice President Clinical and Nonclinical R&D Ferring Pharmaceuticals
Fredrik Andersson, PhD	Senior Director, Global Health Economics and Outcomes Research, Ferring Pharmaceuticals Associate Professor at the University of Linkoping, Sweden
Leslie Krause, MD	Specialist Director, Global Pharmacovigilance Ferring Pharmaceuticals
Egbert van der Meulen, PhD	Senior Director, Global Biometrics Ferring Pharmaceuticals

Nocturia due to Nocturnal Polyuria

Eric Rovner, MD

Professor of Urology

Director Voiding Dysfunction and Female Urology and Urodynamics

Medical University South Carolina

Presentation Overview

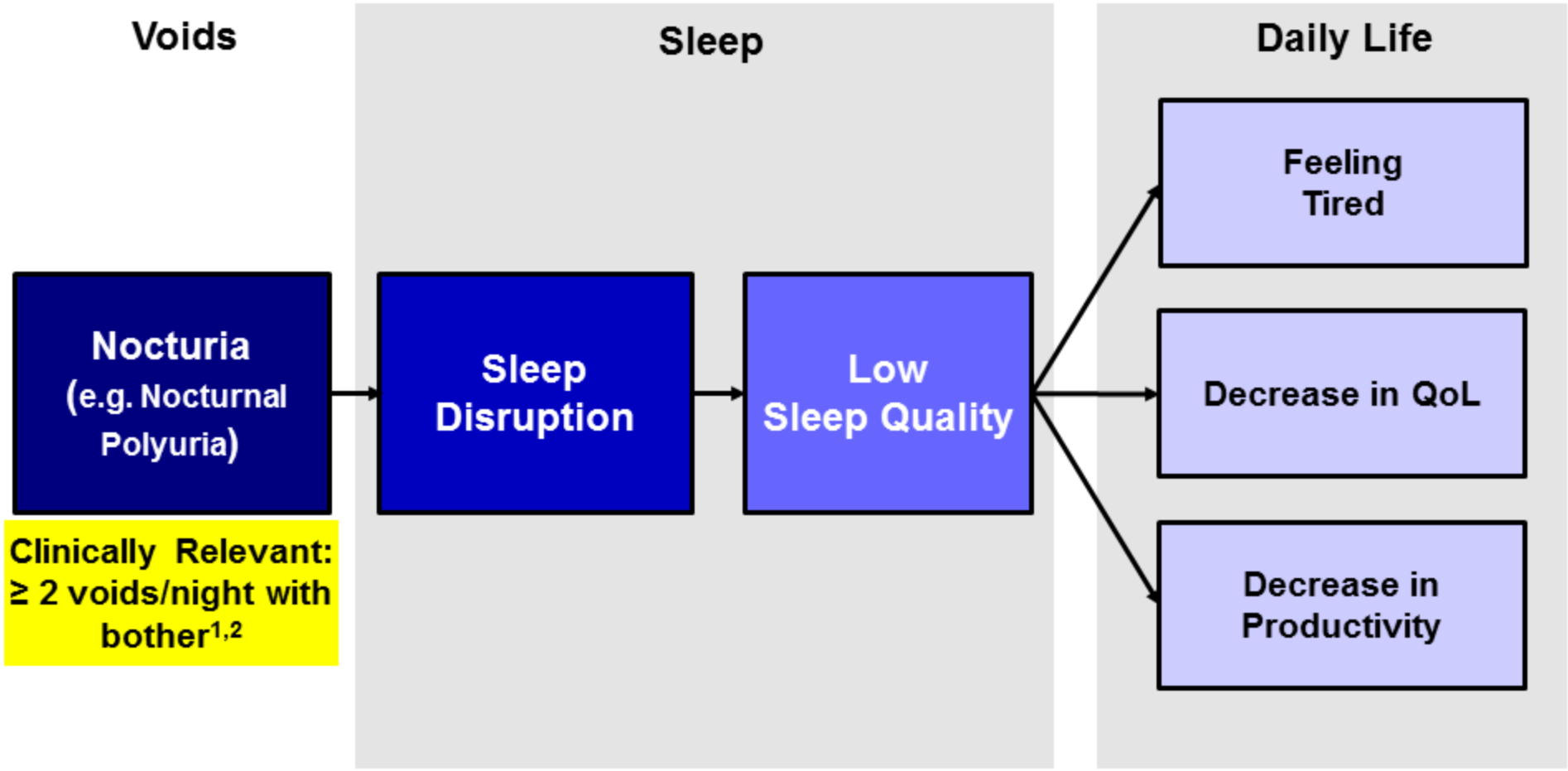
- Nocturia symptoms
  - Threshold for clinical relevance
  - Patient burden
  - Causes
- Nocturia due to nocturnal polyuria (NP)
  - Target treatment population
  - Diagnosis algorithm
- Limitations of current treatment options
  - Current use of desmopressin in U.S.

Nocturia is the Complaint of Waking at Night to Urinate

- Can result from nocturnal polyuria with or without other lower urinary tract conditions (e.g. BPH, OAB, etc.)
- Occurs in men and women of all ages[1]
- Becomes more frequent with age[1]
- Threshold of 2 or more voids at night is associated with significant bother and disease burden[2,3]

1. CDC, NHANES, 2009
2. Kupelian et al., 2011
3. Tikkininen et al., 2010

Significant Bother and Disease Burden with Nocturia ≥ 2 voids/night



1. Kupelian et al., 2011
2. Tikkininen et al., 2010

Pathophysiology of Nocturia Can be Urological or Non-Urological/Medical

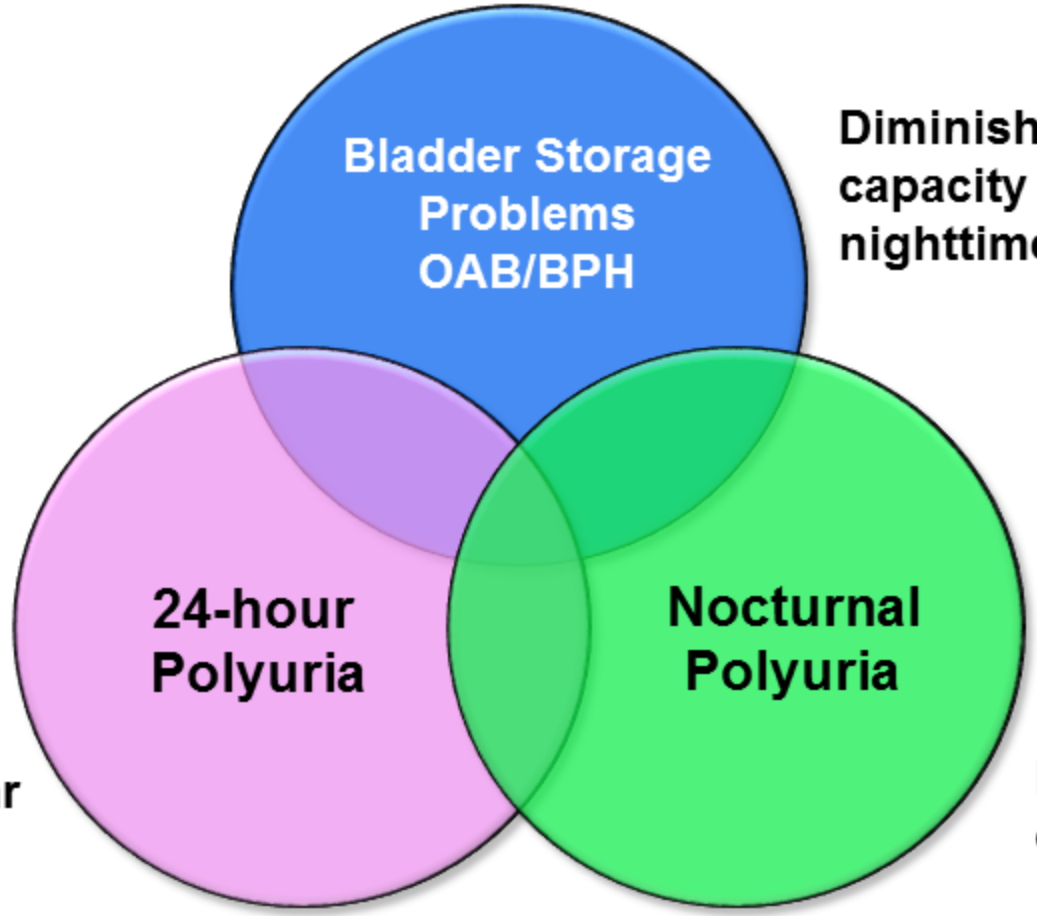
Urological

- Diminished bladder capacity
  - Overactive bladder (OAB)
  - Bladder outlet obstruction (BOO)
    - Benign prostate hyperplasia (BPH)
  - Gynecologic abnormality
  - Neurogenic bladder

Non-Urological or Medical

- 24-hour polyuria
  - Uncontrolled diabetes mellitus, insipidus
  - Primary polydipsia
- Nocturnal polyuria
  - Heart disease, sleep apnea, venous disease etc.
  - NP due to AVP dysregulation

Pathophysiology of Nocturia: 3 Broad Categories*



Diminished bladder capacity during nighttime sleep

>2,800 mL/24 hr

Night volume: >33% of daily total volume

*Not intended to represent true prevalence or overlap

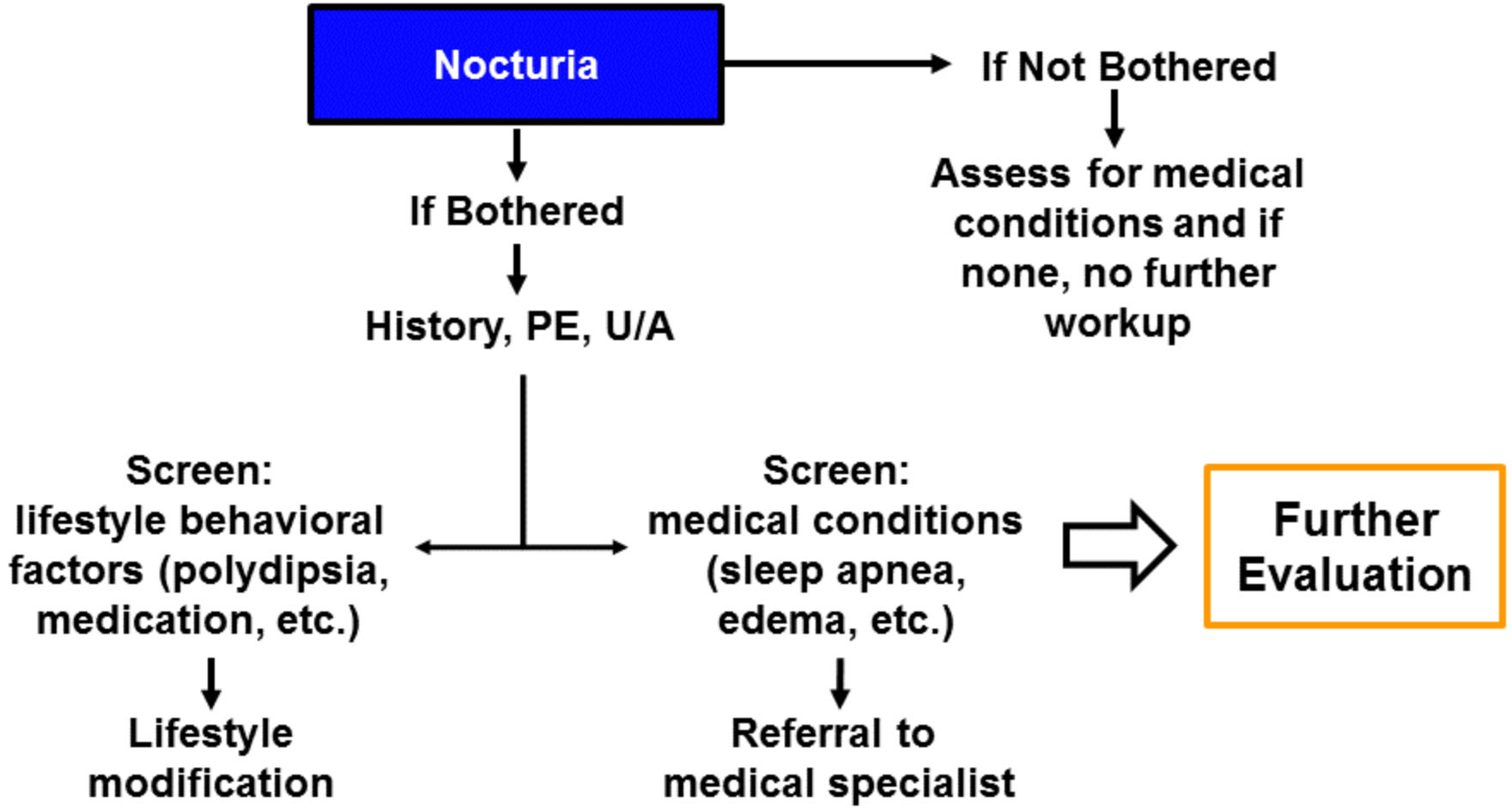
Rembratt et al., 2002

Target Treatment Population: Nocturia due to Nocturnal Polyuria (NP)

- Nighttime urine production in excess of 33%*
  - Not due to polydipsia/24 hour polyuria or comorbid medical conditions that require treatment
- Patients with NP have other conditions of the lower urinary tract (OAB, BPH, etc.)

*International Continence Society

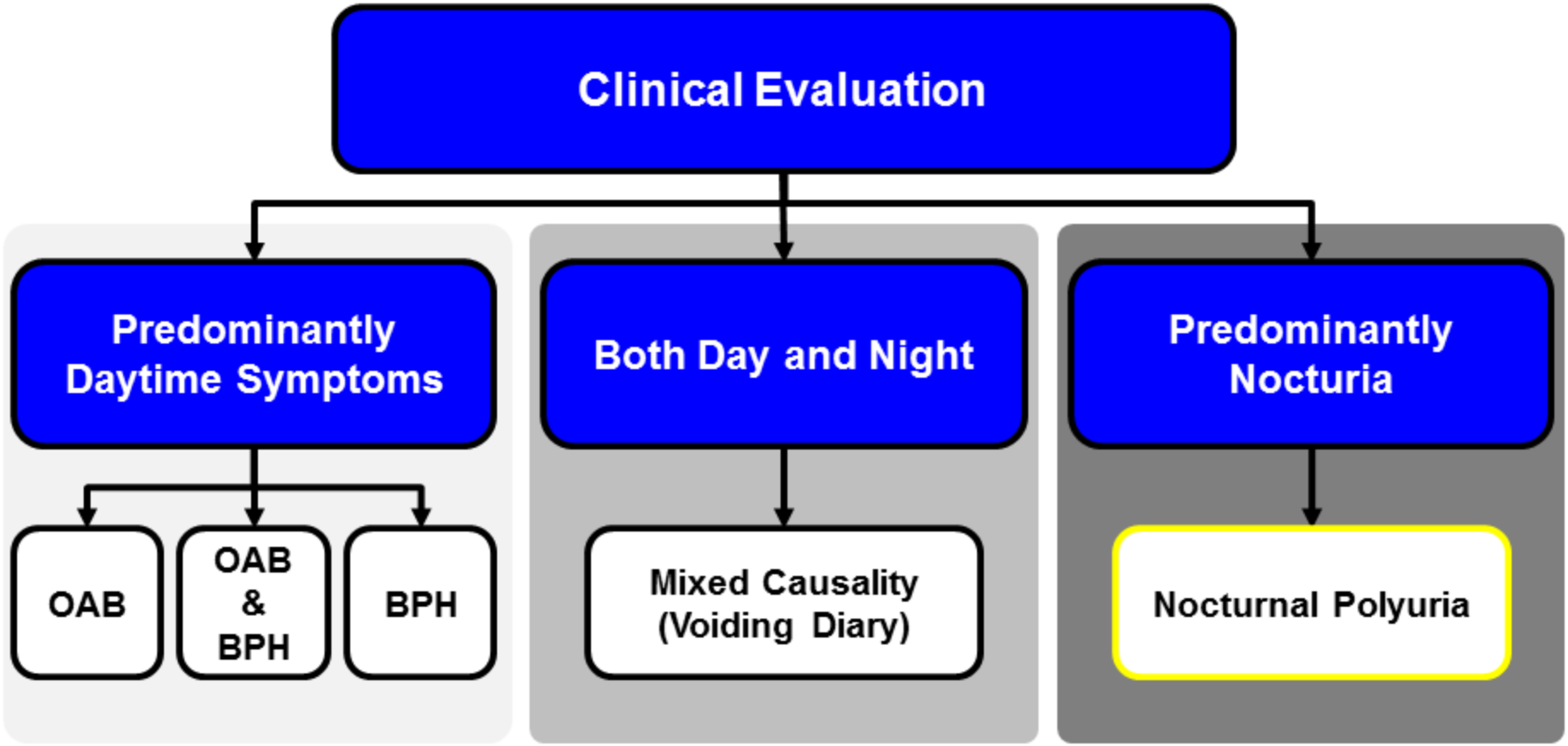
Nocturia due to Nocturnal Polyuria is a Diagnosis of Exclusion



Van Kerrebroeck et al., 2014

PE: Physical Examination, U/A: Urine Analysis, PVR: Post Void Residual

Further Evaluation to Differentiate Nocturnal Polyuria from OAB or BPH



Urological Treatment Approaches Do Not Address Nocturia due to Nocturnal Polyuria

Drug Classes	FDA Approved Indications*		
	OAB	BPH	Nocturia
Antimuscarinics	✓		NO
Alpha blockers		✓	NO
5-ARI		✓	NO
Beta 3 agonists	✓		NO
Antimuscarinic + alpha blocker	✓	✓	NO
5-ARI + alpha blocker		✓	NO

*Package inserts for corresponding drug classes

Desmopressin Recommended in Multiple Guidelines

- American Urological Association BPH guideline[1]
  - "Nocturia should be managed… by reducing fluid intake, and that other treatments, such as desmopressin, can also be considered."
- International Consultation on Incontinence (ICI)[2]
  - Oxford level 1 evidence, Grade A recommendation
- Recommended/included in guidelines from
  - European Association of Urology (EAU)[3]
  - International Consultation on Urological Diseases (ICUD)[4]
  - UK National Institute for Health and Clinical Excellence (NICE)[5]
- FDA-approved in U.S. only for other indications at higher doses

1. McVary et al., 2010
2. Abrams et al., 2013
3. Oelke et al., 2013
4. Wein, 2014
5. Smith et al., 2013

Nocturia due to Nocturnal Polyuria An Unmet Medical Need

- NP is a main cause of nocturia symptoms
- Can coexist with other conditions (OAB, BPH)
- Can result in high bother and patient burden if ≥ 2 awakenings/night to void
- Patient should be treated with antidiuretic
- Defined diagnostic/management algorithms
- Need effective, safe and appropriately labelled treatment

Efficacy Results

Jens Peter Norgaard, MD, DMSc
Professor of Urology
University of Aarhus, Denmark
Global Scientific Affairs, Urology
Ferring Pharmaceuticals

Overall Clinical Development Program Led to Efficacious, Safe Treatment in Target Population

- Nine phase 3 studies from 1997-present
- Early NOCTUPUS trials
  - "Enriched" for NP as recommended by FDA
  - Higher treatment effect
- Recent NOCDURNA trials
  - Population reflects clinical practice
  - 90% NP population through medical history
- Overall goal: maximize safety, maintain efficacy

First Study of Melt Formulation: 4 Doses Against Placebo (CS29)

CS29/31

Randomized, Placebo-Controlled, Multiple Dose Study (Randomized N=799)

Doses: 10, 25, 50, 100 µg

Co-Primary Endpoints

- Change from Baseline to Day 28 in Mean Number of Nocturnal Voids
- ≥ 33% Responders

CS31: Extension

CS40 (Women)

Randomized, Placebo-Controlled, Single Dose Study (Randomized N=268)

Doses: 25 µg

Co-Primary Endpoints

- Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Voids
- ≥ 33% Responders

CS41 (Men)

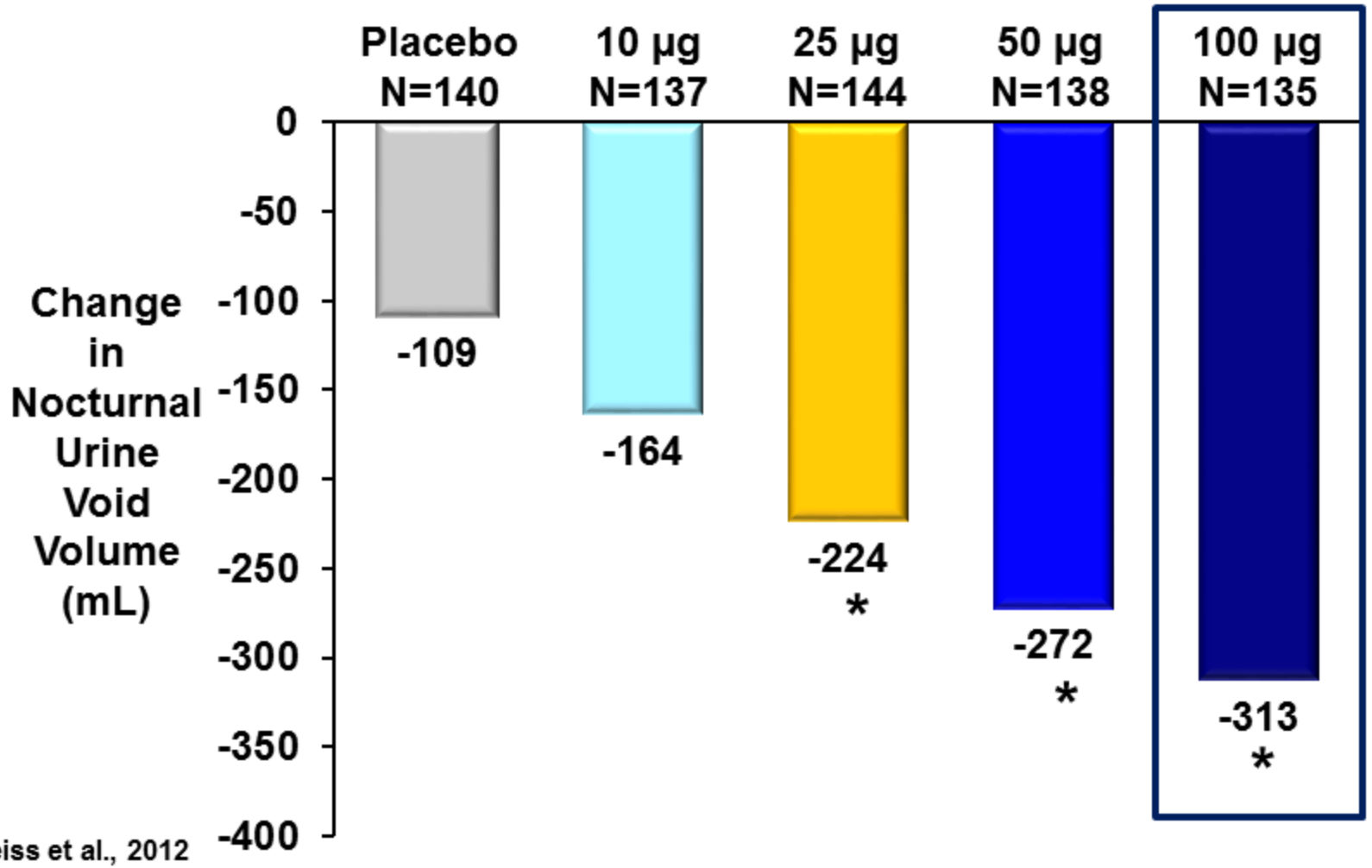
Randomized, Placebo-Controlled Multiple Dose Study (Randomized N=395)

Doses: 50, 75 µg

Co-Primary Endpoints

- Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Voids
- ≥ 33% Responders

Clear Dose Response in Decrease in Mean Volume of Nocturnal Urine (CS29)

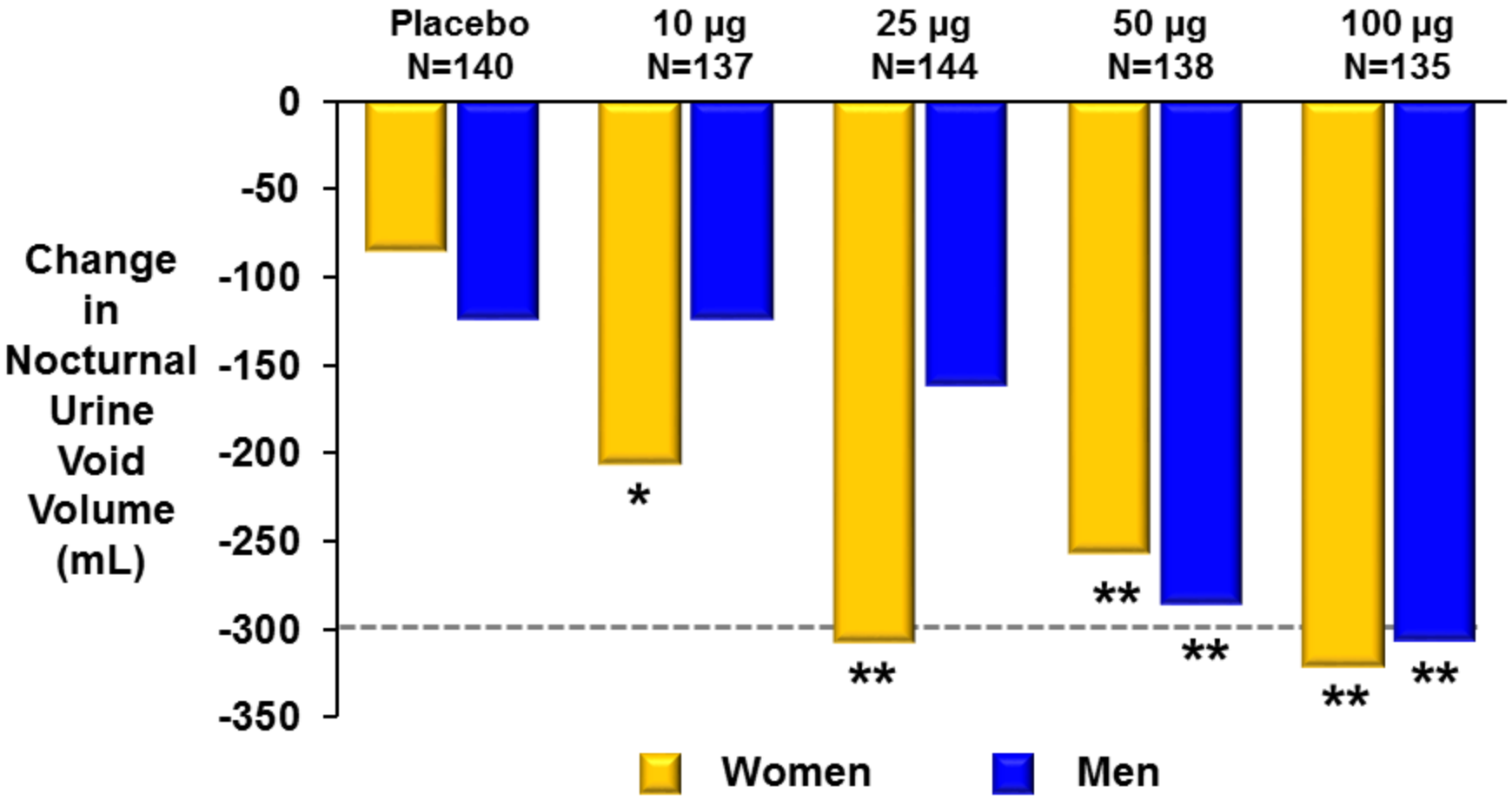


Weiss et al., 2012

*Statistically significant difference versus placebo

CS29 studied both women and men

Pharmacodynamic Effect at Lower Doses in Women Than in Men (CS29)



Weiss et al., 2012

*p<0.05; **p<0.01 NOCDURNA vs placebo

CS29 studied both women and men

CS40/CS41: Key Confirmatory Trials

CS29/31

Randomized, Placebo-Controlled, Multiple Dose Study (Randomized N=799)

Doses: 10, 25, 50, 100 µg

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- Change from Baseline to Day 28 in Mean Number of Nocturnal Voids
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CS41 (Men)

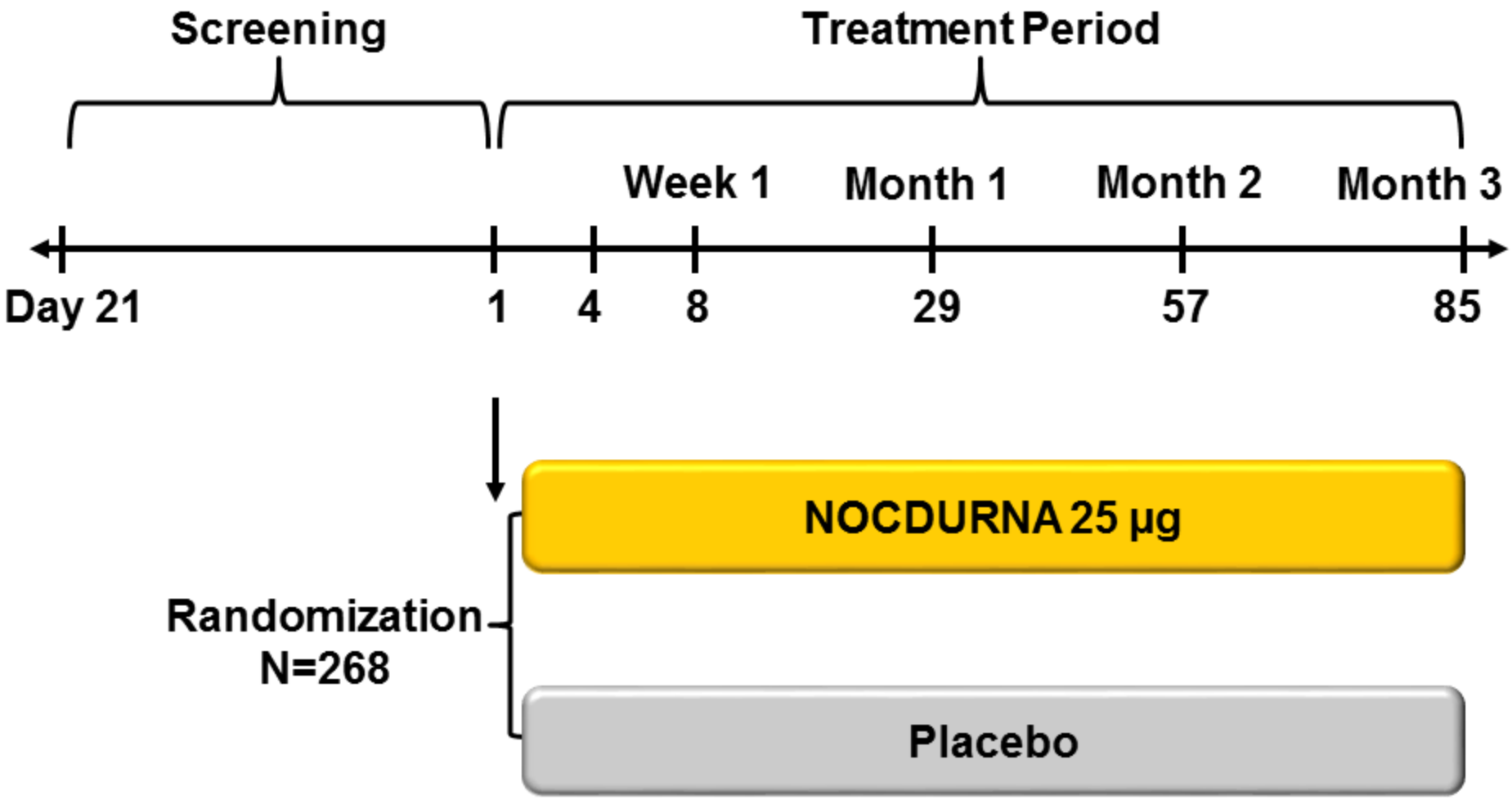
Randomized, Placebo-Controlled Multiple Dose Study (Randomized N=395)

Doses: 50, 75 µg

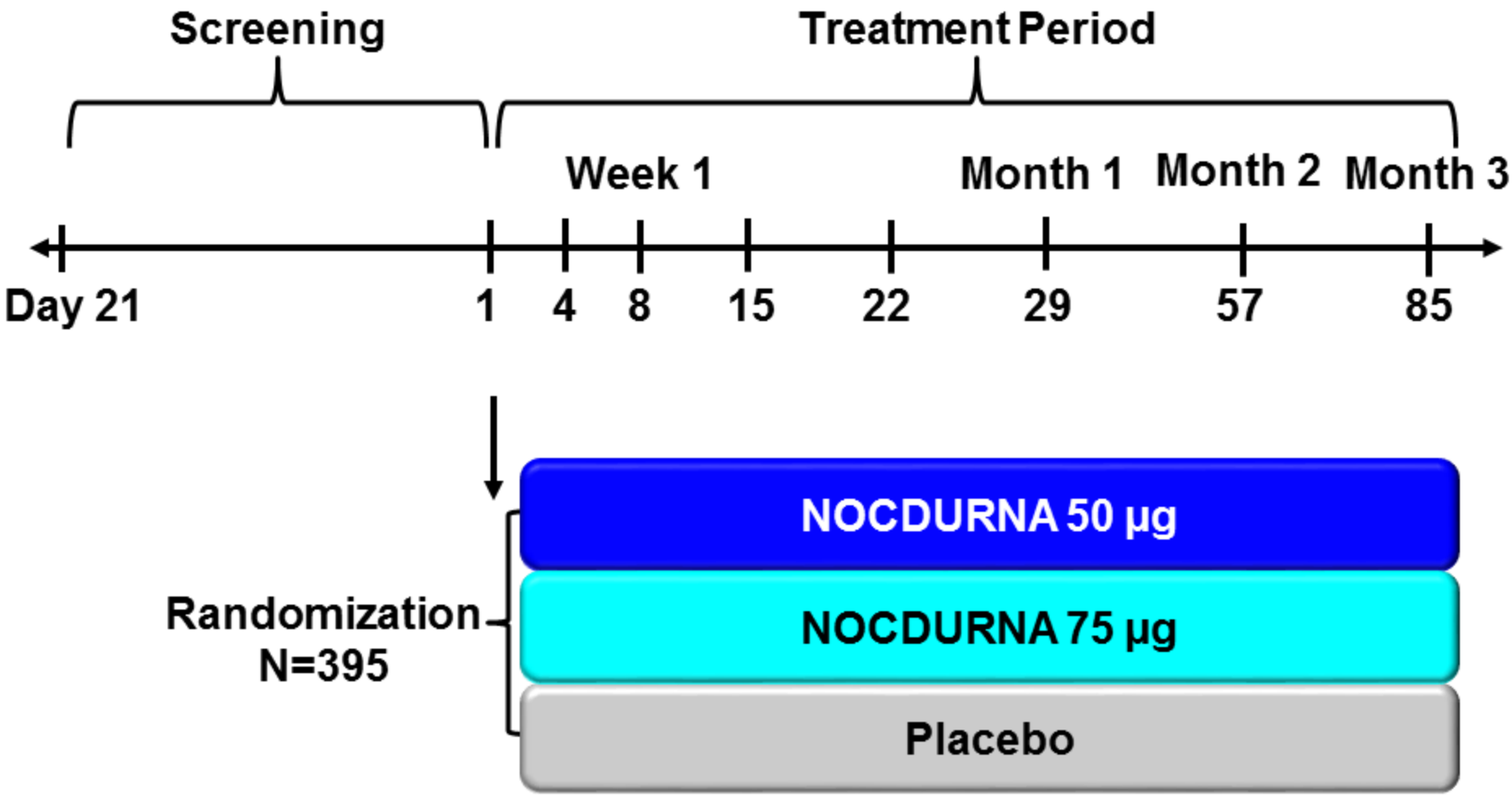
Co-Primary Endpoints

- Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Voids
- ≥ 33% Responders

Trial Design of CS40 in Women



Trial Design of CS41 in Men



Key Inclusion Criteria

- Same in CS40 and CS41
- ≥ 2 voids per night[1,2]
  - Determined by 3-day frequency-volume chart during screening period

1. Kupelian et al., 2011
2. Tikkinen et al., 2010

Key Exclusion Criteria

- Evidence of severe daytime voiding dysfunction causing bladder related nocturia (avoiding significant diminished bladder capacity)
  - Urge urinary incontinence, urgency or frequency (OAB)
  - Suspicion of bladder outlet obstruction (BPH)
- Underlying medical conditions associated with nocturia due to nocturnal polyuria, such as
  - Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
  - Uncontrolled Diabetes Mellitus
  - Renal insufficiency
  - Suspicion or evidence of cardiac failure
  - Sleep apnea

Three Categories of Efficacy Endpoints Demonstrate Clinical Relevance

- Co-primary endpoints
- Secondary endpoints
- Supportive endpoints – QoL and sleep

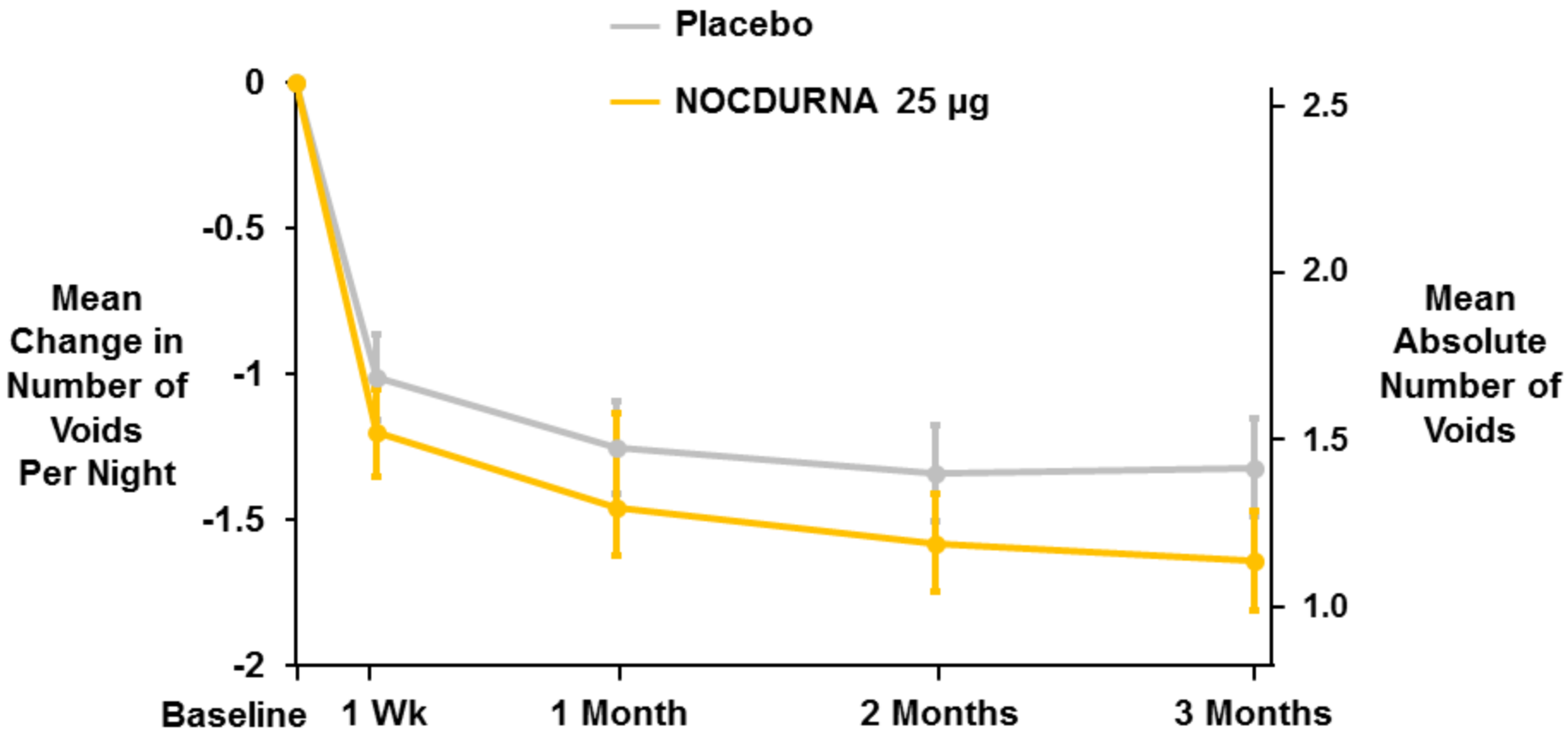
CS40/CS41: Co-Primary Endpoints Analyzed Longitudinally

- All data used during 3 months in a repeated measures model to avoid spurious results at selected time point
- Studies powered to show statistically significant effect on both co-primary endpoints

CS40/CS41: Similar Void Parameters at Baseline Between Groups

- Average of 2.9 voids per night
- Mean time to first nocturnal void was approximately 2.5 hours (145 min)
- ~90% of patients had clinically significant nocturnal polyuria
- Mean baseline NPI ≥ 45%

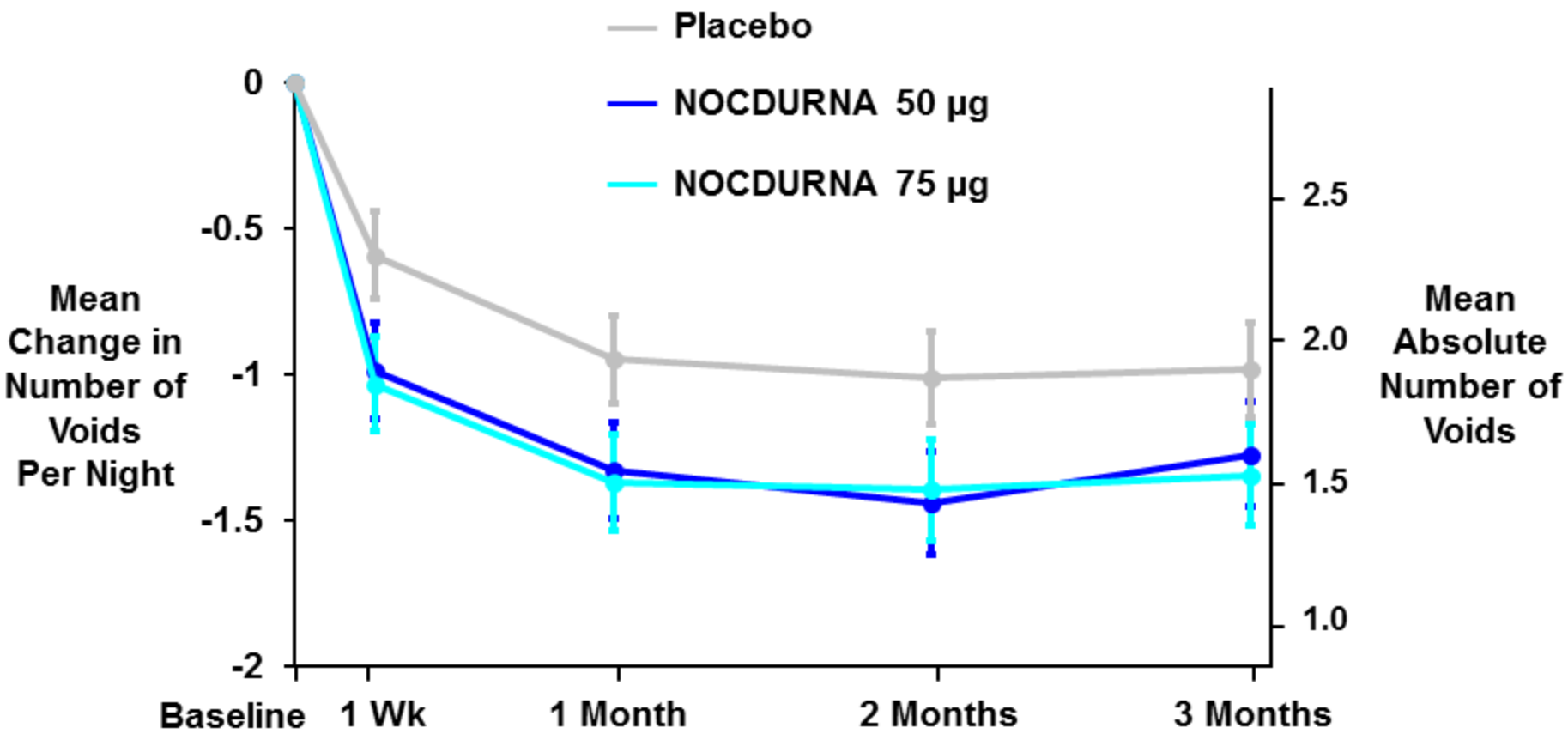
NOCDURNA Met Co-Primary in CS40 (Women): Mean Decrease in Nocturnal Voids



25 µg vs placebo: Δ=0.22, p=0.028

Longitudinal Analysis (95% CI)

NOCDURNA Met Co-Primary in CS41 (Men): Mean Decrease in Nocturnal Voids

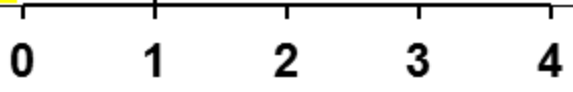


50 µg vs placebo: Δ=0.37, p=0.0003
75 µg vs placebo: Δ=0.41, p<0.0001

Longitudinal Analysis (95% CI)

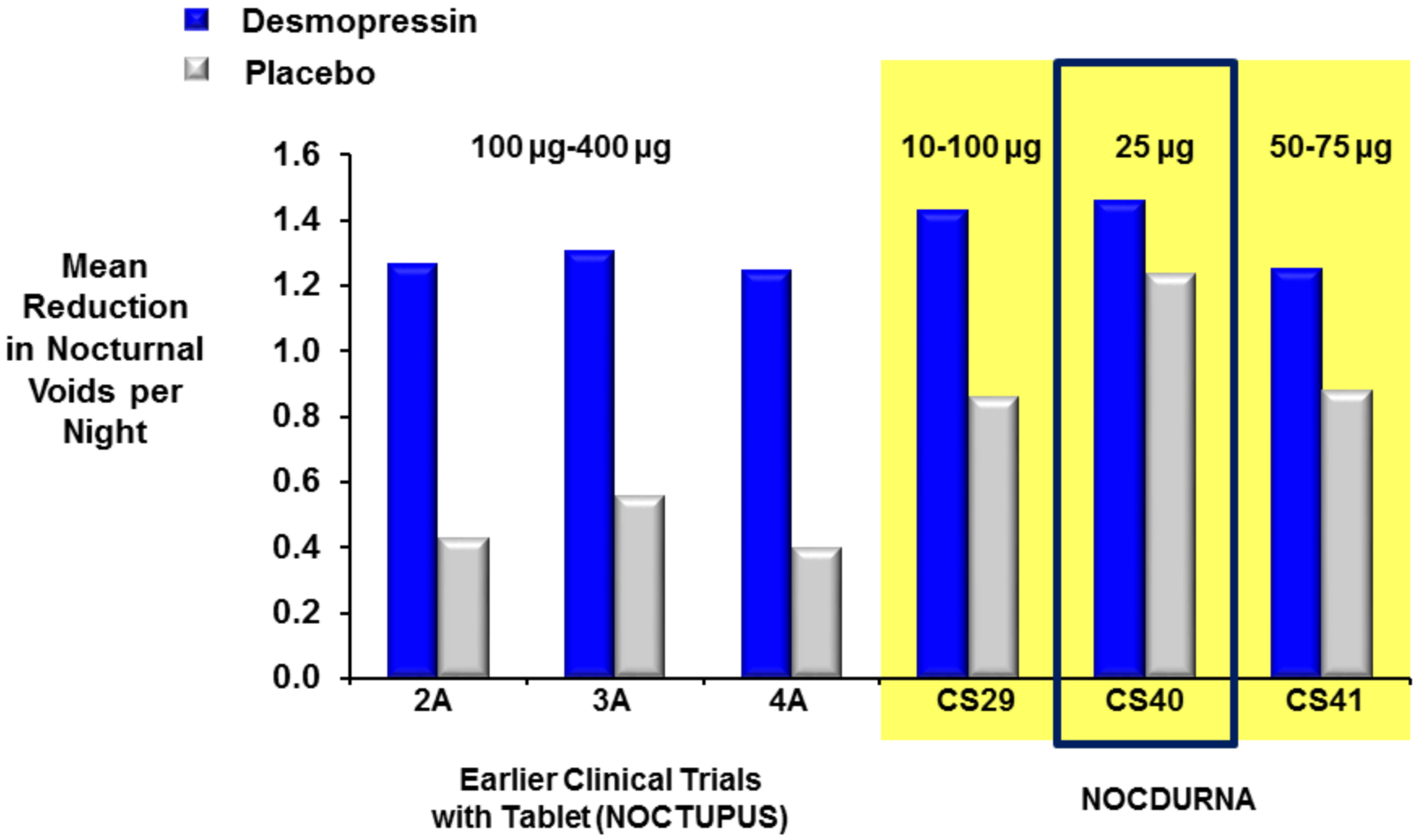
Co-Primary CS40 and CS41: Doubled Odds of Achieving ≥ 33% Reduction in Voids

Study		N	Odds	Odds Ratio	Favors NOCDURNA	p-value
CS40 (Women)	25 µg	130	3.23	1.85		0.0061
	Placebo	125	1.75			
CS41 (Men)	50 µg	116	2.01	1.98		0.0009
	Placebo	142	1.02			
	75 µg	122	2.08	2.04		0.0004
	Placebo	142	1.02			



Longitudinal Analysis (95% CI)

Change from Baseline with NOCDURNA Similar to Earlier Trials



Several Factors May Contribute to High Placebo Effect

- Commonly seen in lower urinary tract dysfunction studies
- No placebo or active run-in before randomization
- Regression to the mean
- Inclusion of lifestyle modifications and behavioral reinforcement during trials
- Multiple questionnaires and diaries

Three Categories of Efficacy Endpoints Demonstrate Clinical Relevance

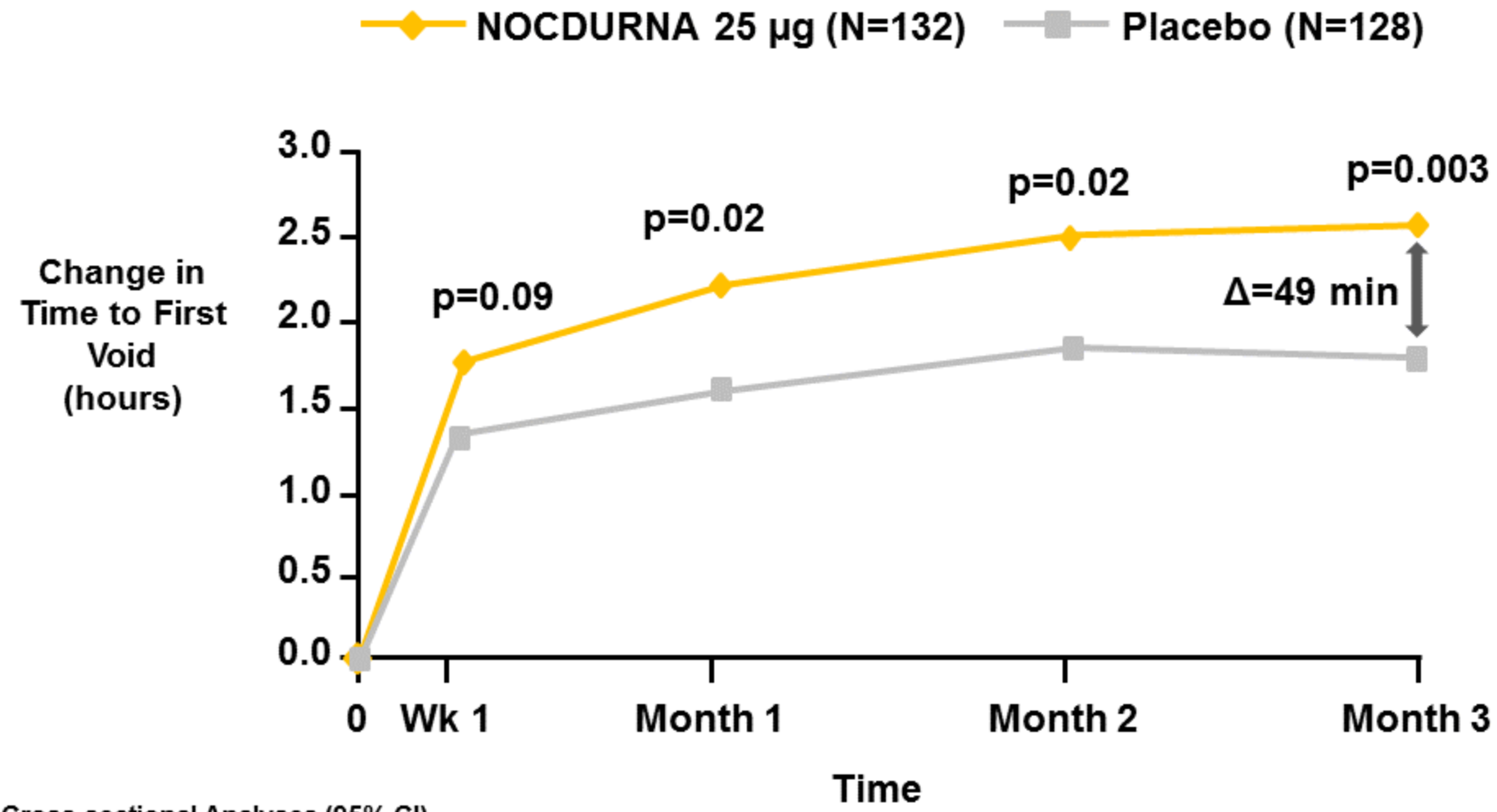
- Co-primary endpoints
- Secondary endpoints
- Supportive endpoints – QoL and sleep

CS40/CS41: Secondary Endpoints Analyzed at End of Treatment*

- Change in mean number of nocturnal voids
- Proportion of 33% responders
- Mean time to first nocturnal void
- Mean nocturnal urine volume
- Mean 24-hour urine volume

*Cross-sectional data analyzed at month 3

CS40 (Women): Sustained Increase in Time to First Nocturnal Void

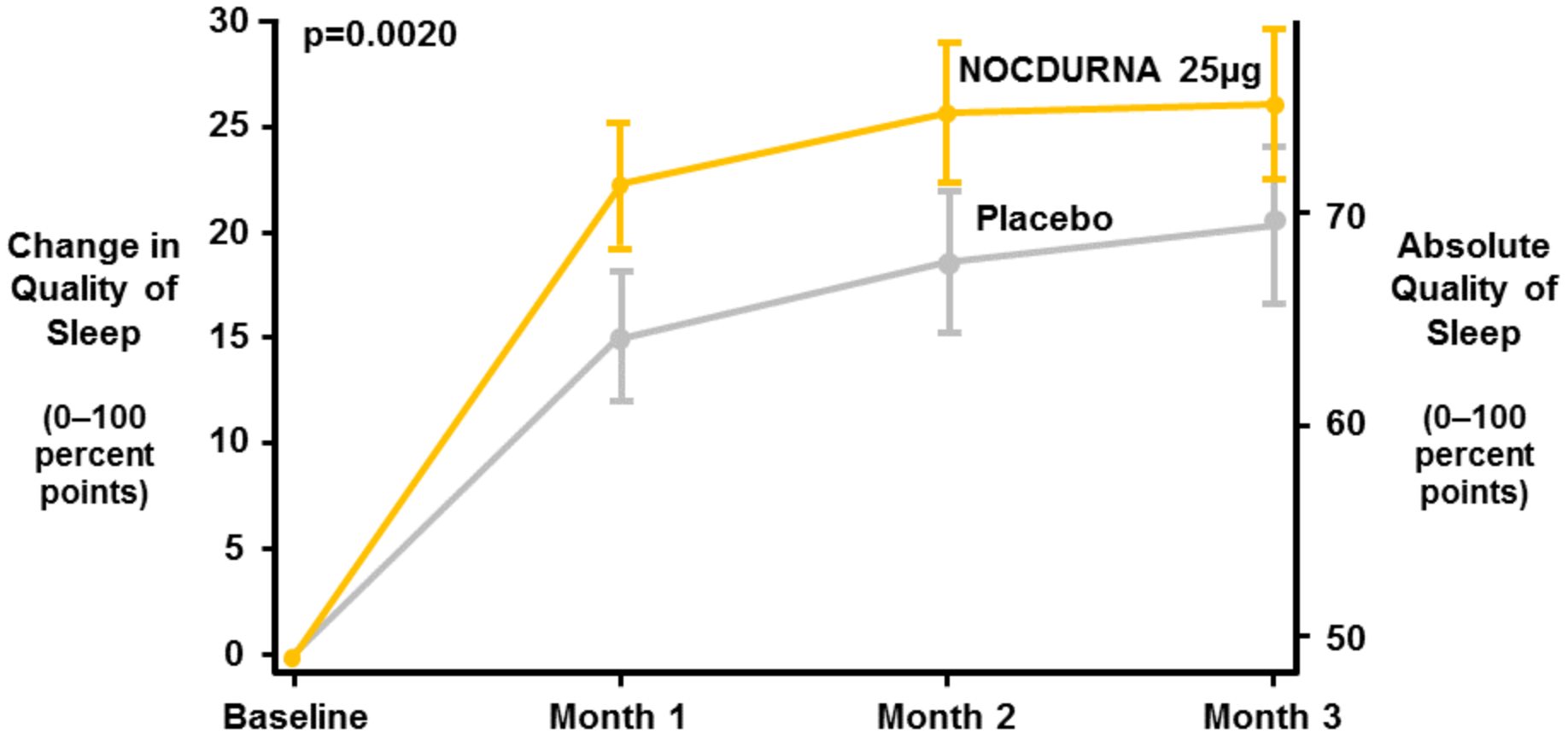


Cross-sectional Analyses (95% CI)
Sand PK et al., 2013

Three Categories of Efficacy Endpoints Demonstrate Clinical Relevance

- Co-primary endpoints
- Secondary endpoints
- Supportive endpoints – QoL and sleep

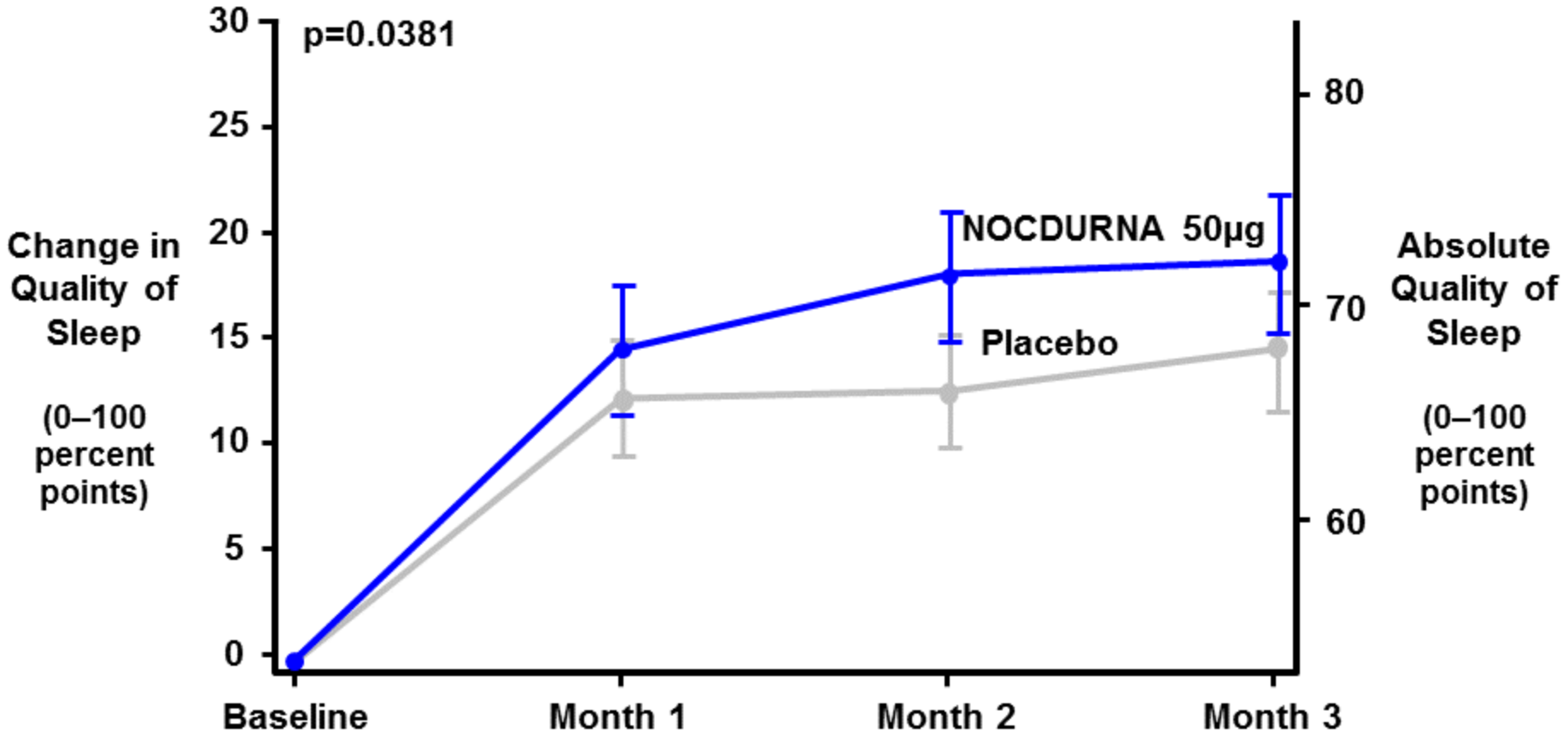
CS40 (Women): Self-Rated Quality of Sleep Improved Consistently Over 3 Months



Treatment Contrast: 6.7% (95% CI: 2.5-10.9%)

Longitudinal Analysis (95% CI)

CS41 (Men): Self-rated Quality of Sleep Improved Consistently Over 3 Months

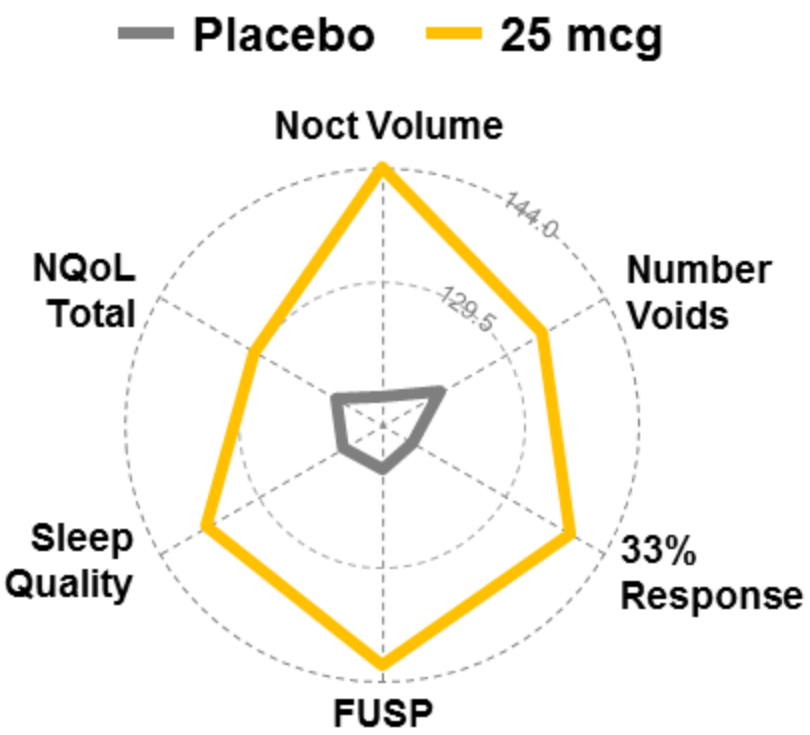


Treatment Contrast: 3.9% (95% CI: 0.22-7.64%)

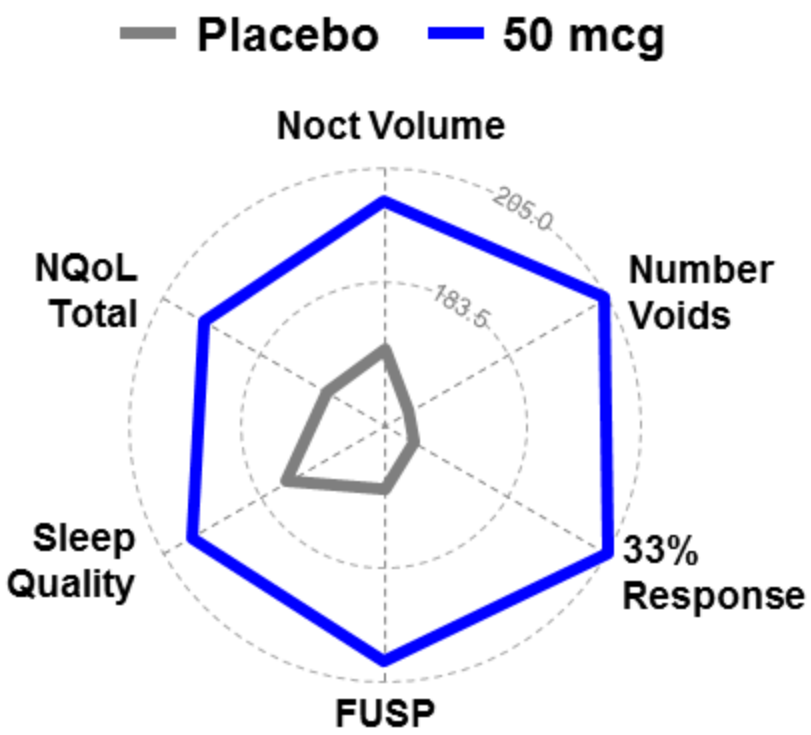
Longitudinal Analysis (95% CI)

NOCDURNA Demonstrated Consistent and Statistically Significant Efficacy Across Key Endpoints in Women (CS40) and Men (CS41)

Women (CS40):
Total Efficacy
p=0.0009 (O'Brien)



Men (CS41):
Total Efficacy
p=0.0006 (O'Brien)



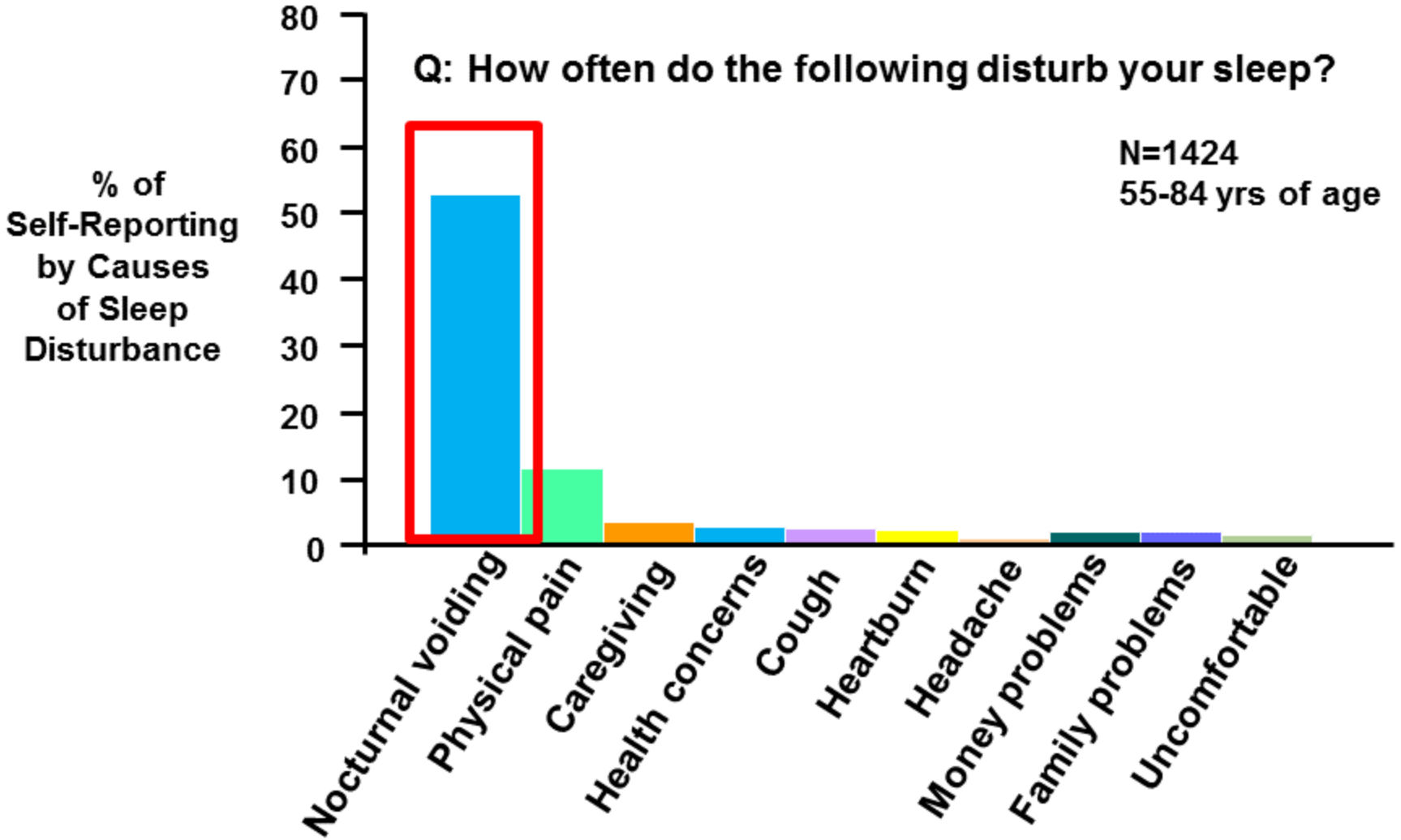
NOCDURNA Consistently Demonstrated Efficacy Across Pivotal Trials

- Three Phase 3 trials: 1443 subjects
- Study population reflects adults (all ages) seeking treatment in clinical practice
- Met co-primary endpoints agreed upon with FDA in SPA with statistical significance

Additional Clinical Relevance/Sleep

Donald Bliwise, PhD
Professor of Neurology
Emory University School of Medicine
Atlanta, GA

Nocturnal Voiding: Leading Self-Attributed Cause of Sleep Disturbance



Bliwise DL et al. *Sleep Med.* 2009;10(5):540-548.

Factors Known to be Associated With Poor Sleep

Risk Factor	Odds Ratio (95% CI)
Depression	2.49 (1.61, 3.87)
Stroke	2.28 (1.06, 4.89)
Arthritis	1.85 (1.35, 2.55)
Nocturia	1.75 (1.31, 2.35)
Female	1.64 (1.20, 2.23)
Osteoporosis	1.52 (1.01, 2.30)

Multivariable modeling controlling for other self-reported conditions
Bliwise et al., Sleep Med 2009; 10: 540-8

Time to First Void Increased With NOCDURNA

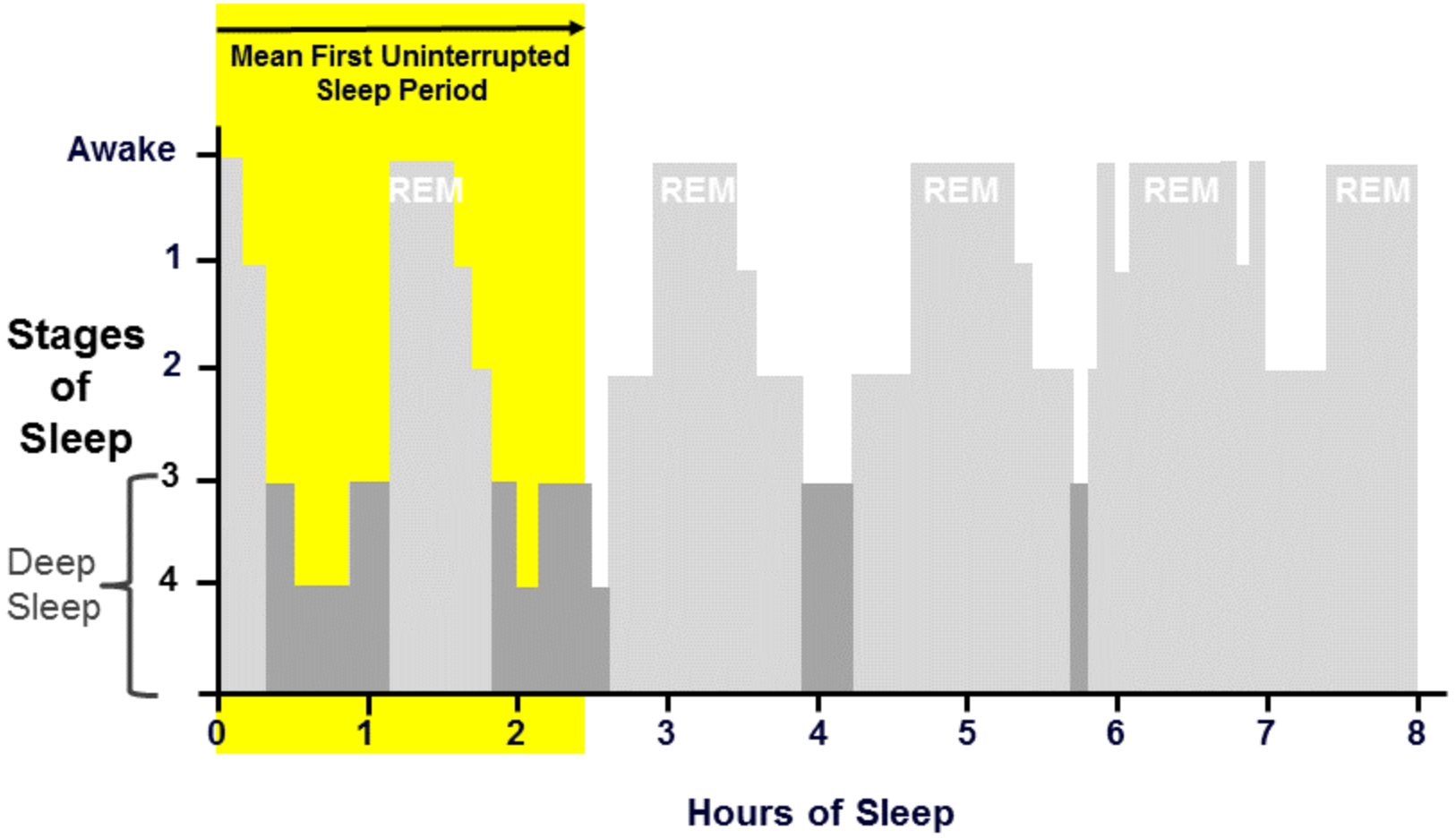
Study	Patient Group	Reduction in # of Nocturnal Voids Relative to Placebo	Increase in Mean Time to 1st Void Relative to Placebo (mins)
CS29[1]	Females	0.34	76
CS29[1]	Males	0.29	32
CS40[2]	Females	0.22	49
CS41[3]	Males	0.37	39

1. Weiss et al., 2012
2. Weiss et al., 2013
3. Sand et al., 2013

CS40/41 data based on longitudinal effect estimates during 3 months; CS29 data are based on the effect estimate at D28.

Potential Impact of Nocturia on Sleep Stages

Stages 3 and 4 May be Interrupted by First Voiding Episode



van Kerrebroeck et al., 2007

Stages 3/4 Reduced for Entire Night with Early First Voiding Episode

Sleep Measure	First Void *During* First 2 Sleep Cycles Min (± SD)	First Void *After* First 2 Sleep Cycles Min (± SD)	p-value
Total sleep	306 (54)	330 (47)	NS
Stages 1 and 2 sleep	170 (41)	171 (33)	NS
Stages 3 and 4 sleep	37 (24)	56 (22)	0.023
REM sleep	95 (35)	103 (25)	NS

Torimoto et al., 2012
Torimoto et al., 2013

Time to First Void Associated with Conventional Measure of Sleep Quality (PSQI*) (CS29)

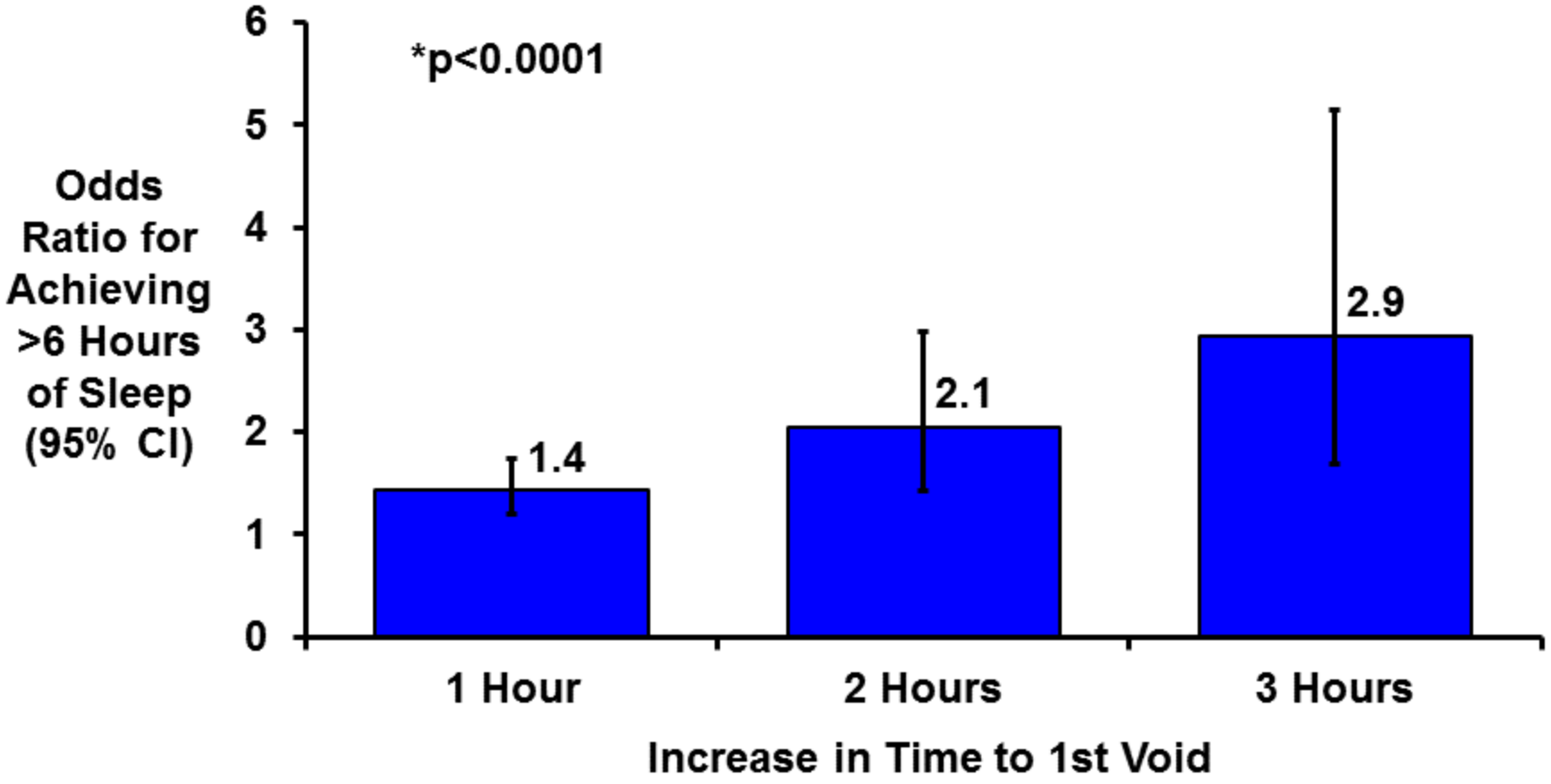
1 hour increase in time to 1st void associated with significant improvement in 7 out of 8 components

PSQI Scale Component	Regression Coefficient	SE	p-value
Global	-0.488	0.054	<0.0001
Sleep Quality	-0.106	0.012	<0.0001
Sleep Latency	-0.079	0.015	<0.0001
Sleep Duration	-0.068	0.013	<0.0001
Sleep Efficiency	-0.102	0.018	<0.0001
Sleep Disturbances	-0.044	0.012	0.0002
Sleep Medication	-0.016	0.016	0.30
Daytime Dysfunction	-0.075	0.014	<0.0001

Bliwise D et al, *Sleep Medicine* 2014, in press

*PSQI: Pittsburgh Sleep Quality Index; data combined across all doses

Increases in Time to First Void are Associated With Greater Odds of Achieving >6 Hours of Sleep (CS29)



Based on GEE re-analyses of first uninterrupted sleep period data in Weiss et al. *Neurourol Urodyn.*, 2012

NOCDURNA May Increase Sleep More than Traditional Sleep Medications

- NOCDURNA increase of uninterrupted sleep relative to placebo: 32-76 minutes

	Treatment Difference (Active vs. Placebo) First 4-6 Hrs of Sleep Period (min)
Eszopiclone (Lunesta)® 3mg[1]	25.0
Doxepin (Silenor)® 6mg[2]	22.2
Zolpidem-MR (Ambien-MR)®[3]	16.0

1. Zammit et al., 2004
2. Roth et al., 2010
3. Roth et al., 2006

Patient Reported Outcomes/QoL

Raymond Rosen, PhD

Chief Scientist

New England Research Institutes, Inc.

Nocturia Quality of Life (N-QOL) Scale: FDA Questions and Concerns

- Content validity
- Recall period
- Consistency of results

N-QoL: Background and Assessment on Content Validity

- Gold standard for QoL assessment in nocturia trials since 2004[1]
- Translated and validated in 29 languages, included in 11 major studies, and included in 40+ peer-reviewed publications
- Content validity confirmed by qualitative interviews with ~100 patients in 2 independent studies[2,3]

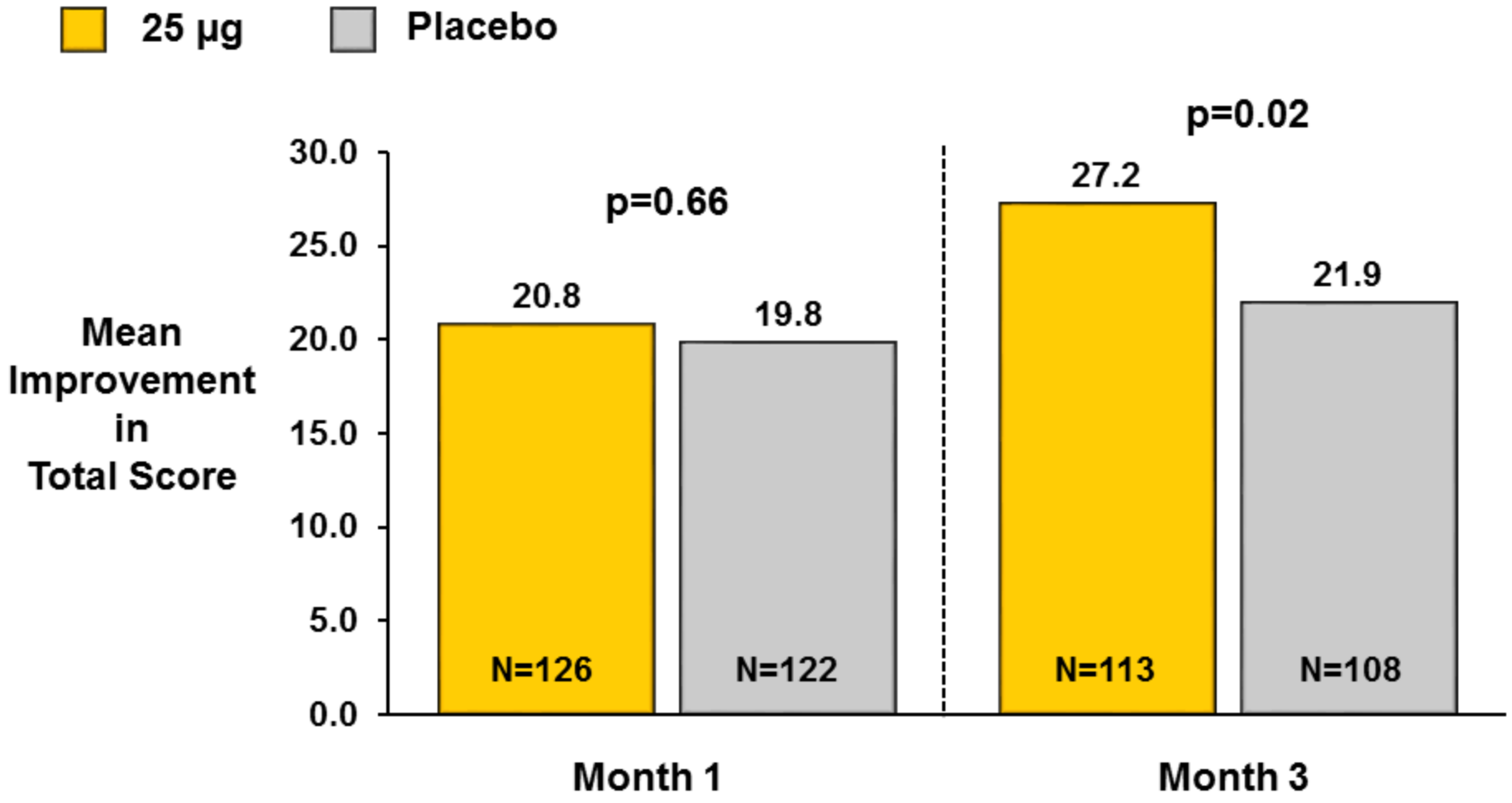
1. Abraham et al., 2004
2. Mock et al., 2008
3. Booth et al., 2010

Suitability of a 2-week Recall Period to Assess Patient Benefit

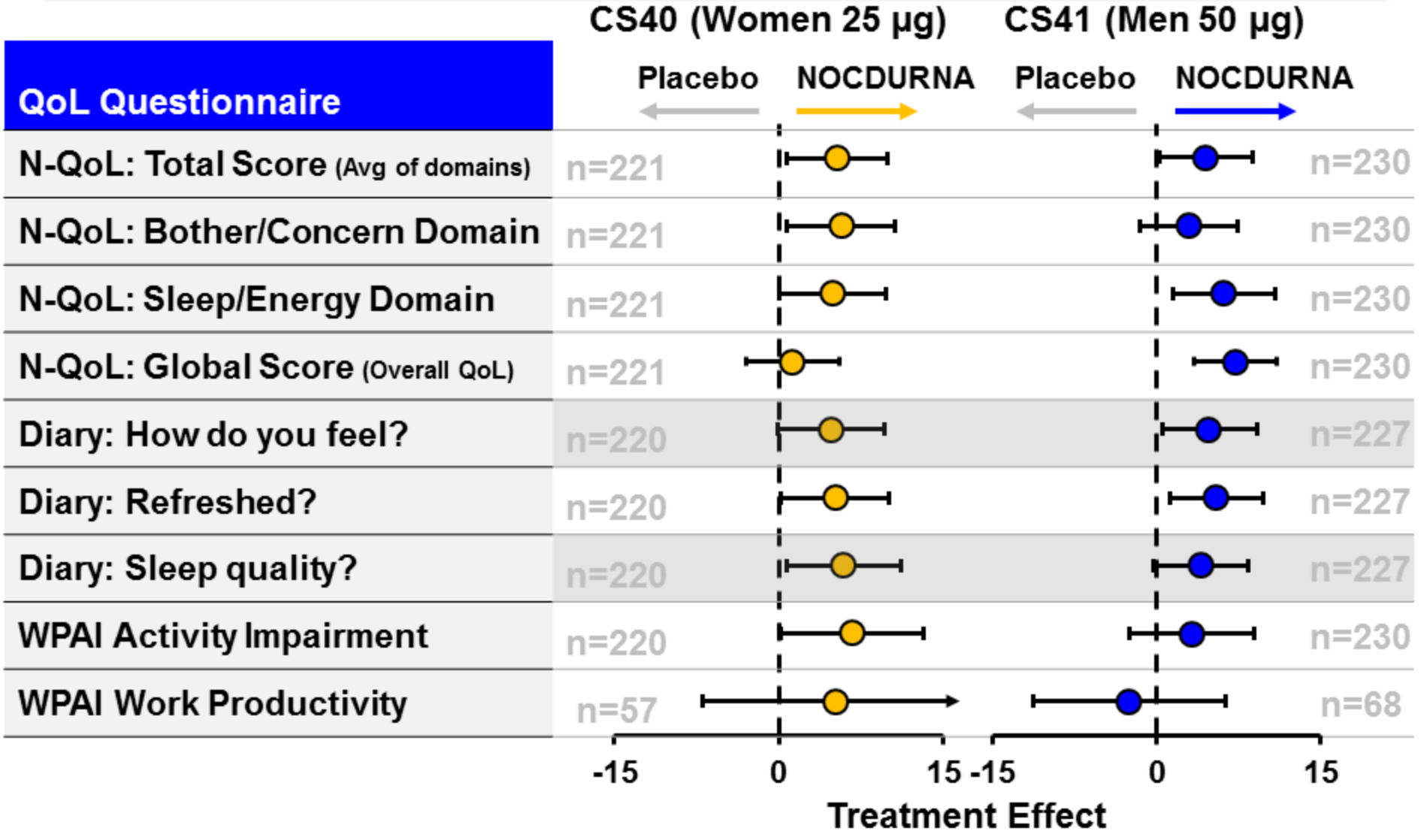
- Optimal recall period depends on disease and type of therapy[1]
- 2 or 4-week recall period is consistently used in research and clinical practice
  - IPSS[2] (BPH) – 1 month
  - DCP[3] (Diabetes) – 1 month
  - AQLQ[4] (Asthma) – 2 weeks
  - PAC-QOL[5] (Constipation) – 2 weeks

1. Norquist et al, 2012
2. Barry et al., 1992; IPSS: International Prostate Symptom Score
3. Fitzgerald et al., 1996; DCP: Disease Control Priorities
4. Juniper et al., 1992; AQLQ: Asthma Quality of Life Questionnaire
5. Marquis et al., 2005; PAC-QoL: The Patient Assessment Constipation-Quality of Life

Consistency of N-QOL Results within and Across Trials: Improvements in Women (CS40) at 1 and 3 Months



Consistency of Patient Benefit Evident Across Multiple QoL Measures



Safety

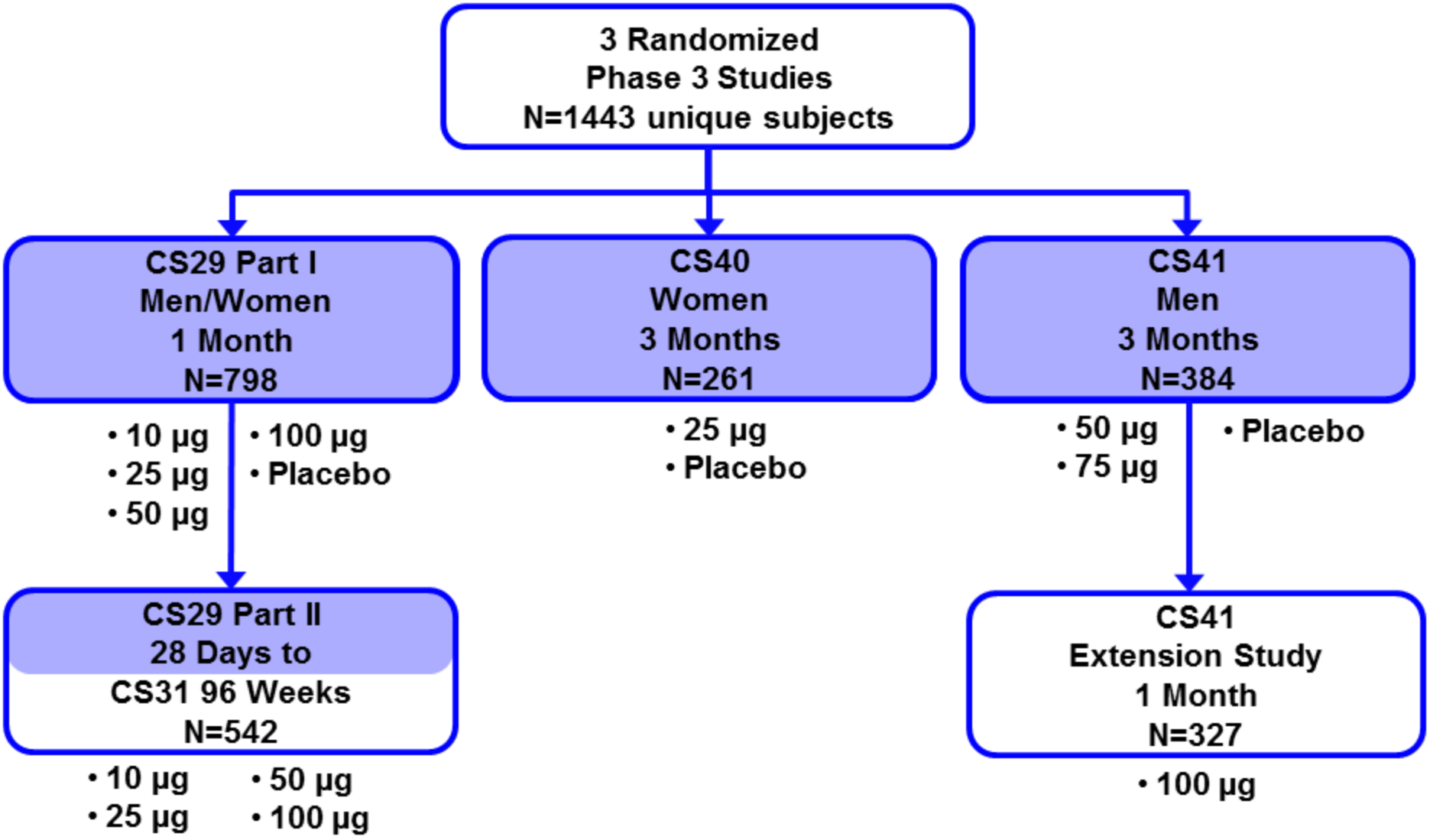
Vladimir Yankov, MD
Vice President
Reproductive Health & Urology
Ferring Pharmaceuticals

Desmopressin: Over 40 Years of Worldwide Use

- Long history of safety use at much higher doses than proposed for NOCDURNA
- Desmopressin cumulative patient exposure for oral formulations:*
  - Oral overall: 4.2 million patient-years
  - Melt: 1.1 million patient-years
  - Oral overall in nocturia: 246,000 patient-years
    - Hyponatremia reporting rate: 2.8 cases/10,000 patient-years (nocturia indication, desmopressin melt and tablet, 60-240 µg doses)
- Melt: reported AEs consistent with known safety profile of tablet

*As of 31 Dec 2013

NOCDURNA Integrated Safety Set



Adverse Events with Incidence ≥ 5% in any Treatment Group – Women (CS40) and Men (CS41)

MedDRA Preferred Terms	CS40 (Women)		CS41 (Men)		
	25 µg N=135	Placebo N=126	50 µg N=119	75 µg N=122	Placebo N=143
	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event	60 (44%)	57 (45%)	46 (39%)	49 (40%)	58 (41%)
Dry mouth	6 (4%)	4 (3%)	4 (3%)	1 (<1%)	7 (5%)
Urinary tract infection	5 (4%)	10 (8%)	5 (4%)	0	0
Upper respiratory infection	4 (3%)	6 (5%)	1 (<1%)	2 (2%)	3 (2%)
Headache	7 (5%)	4 (3%)	6 (5%)	7 (6%)	5 (3%)
Hyponatremia	2 (1%)	1 (<1%)	3 (3%)	5 (4%)	0
Blood sodium decreased	0	0	1 (<1%)	2 (2%)	0

Serious Adverse Events with Incidence ≥ 1% in Any Treatment Group (Integrated Safety Set*)

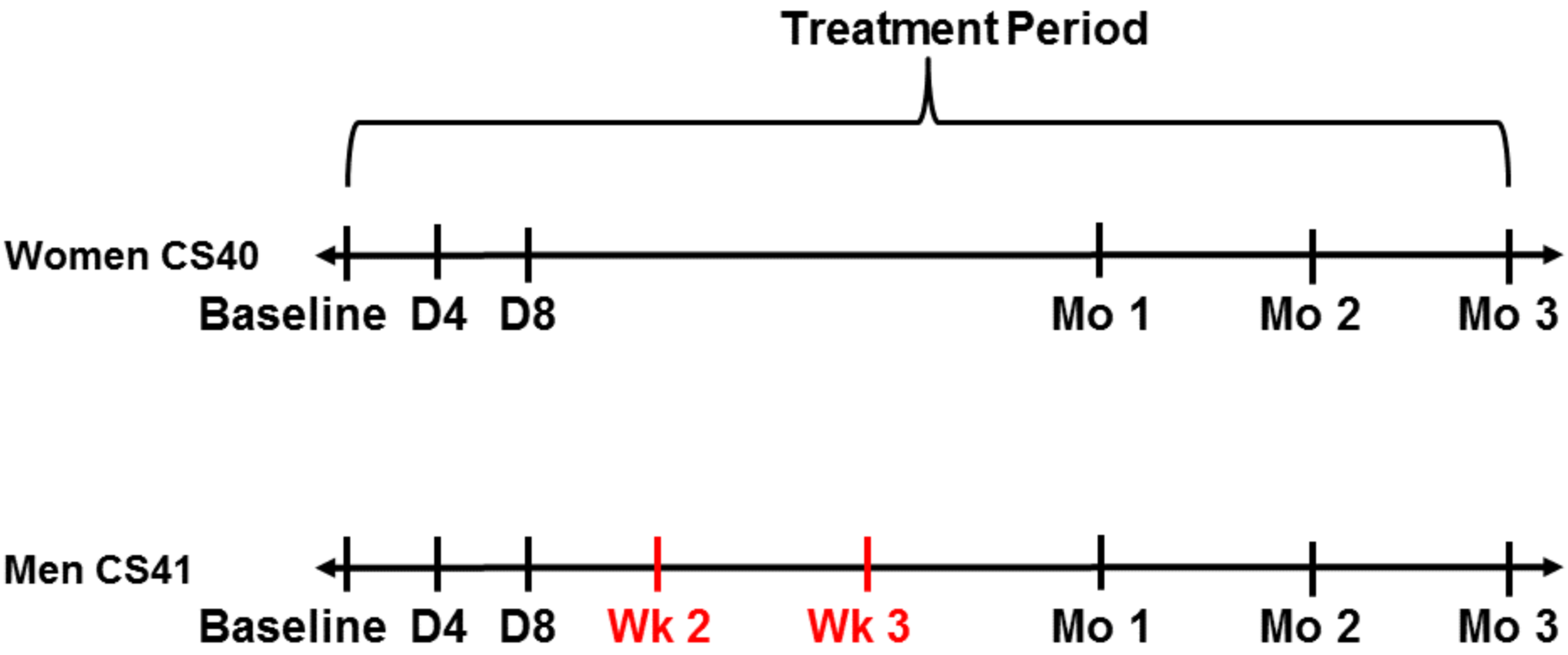
- No deaths in 3-month treatment period

MedDRA Preferred Term	10 µg N=194 n (%)	25 µg N=331 n (%)	50 µg N=311 n (%)	75 µg N=122 n (%)	100 µg N=194 n (%)	Placebo N=429 n (%)
Any SAE	3 (2%)	2 (<1%)	5 (2%)	5 (4%)	3 (2%)	4 (<1%)
Hyponatremia	0	0	2 (<1%)	4 (3%)	0	0

- Serum sodium levels ≤ 125 mmol/L required reporting as SAE (CS40 and CS41)
- All but 1 subject experienced asymptomatic hyponatremia
- All other SAEs: <1%

*CS29, CS40, CS41 combined; males and females combined

Clinical Trial Monitoring Program Utilized in CS40 and CS41



Per Protocol Guidance for Monitoring Serum Sodium

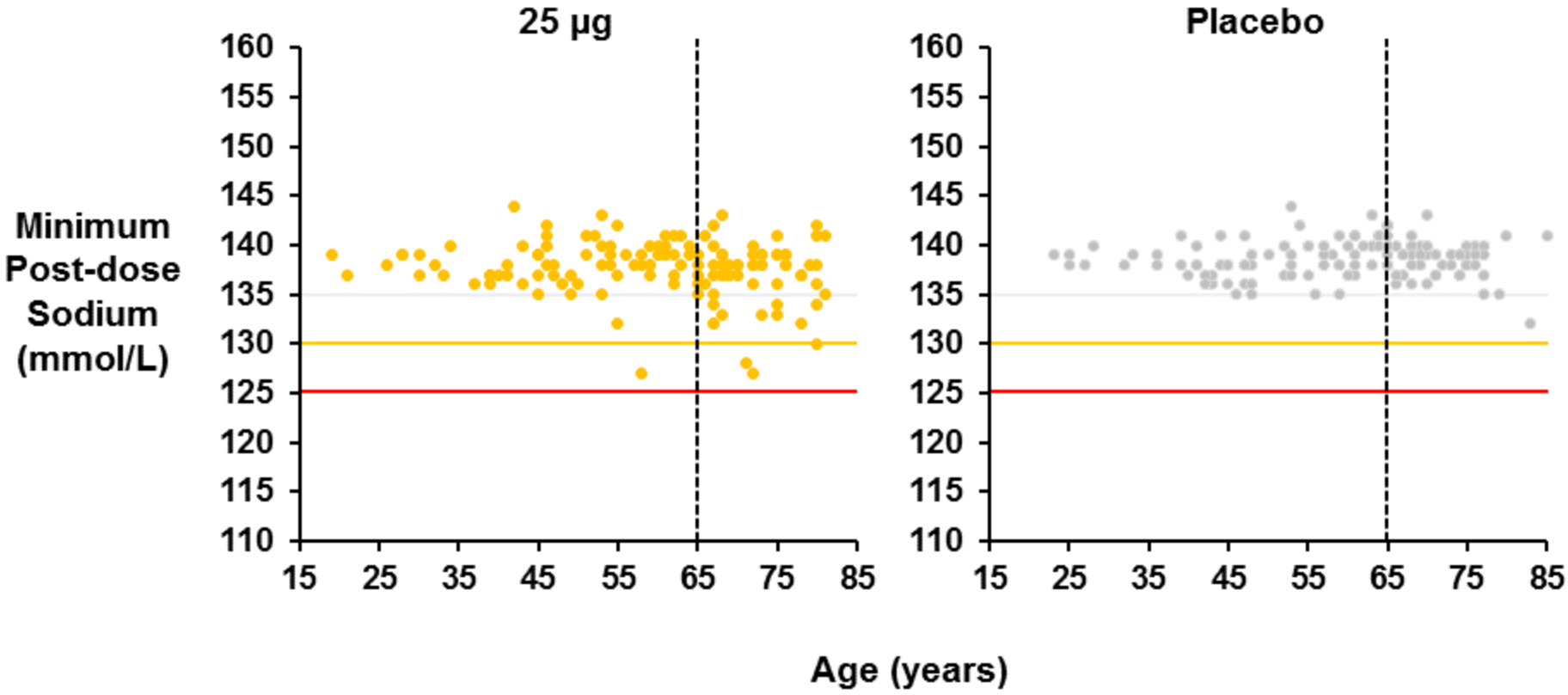
- 126 to 134 mmol/L: subject allowed to remain on treatment; investigator scheduled a follow-up visit
  - If determined as clinically significant by investigator, reported as AE
- ≤ 125 mmol/L: subject discontinued from drug
  - Reported as SAE (except CS29)
- Subjects followed at least until serum sodium values were >130 mmol/L

Hyponatremia: Early Onset, Mild, Reversible in Clinical Trials

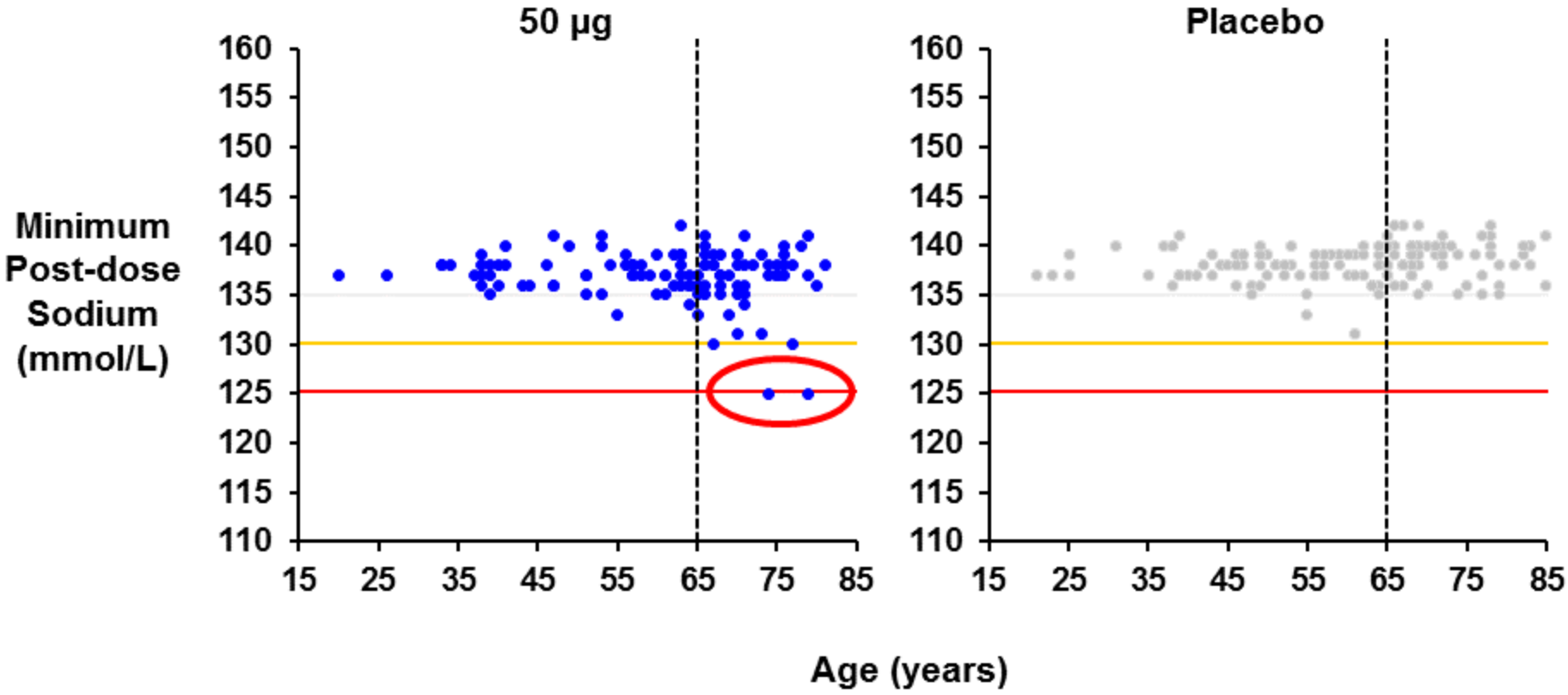
- Baseline serum sodium <135 - predictor
- Study results
  - Dose-dependent
  - Gender-dependent
  - Age-dependent
  - Usually occurs early in treatment
- Low rate*: 0-3% ≤ 125 mmol/L, 0-4% 126-129 mmol/L
- Most asymptomatic
- Transient: sodium returns to normal in 1 to 3 weeks while on treatment in most subjects

*CS40/41, including 75 µg (Men)

CS40: No Females Experienced Serum Sodium Below 125 mmol/L



CS41: No Men Experienced Serum Sodium Below 125 mmol/L at 50 µg Dose



Measures to Further Reduce Risk of Hyponatremia in Clinical Practice

- Proposed sodium monitoring plan
- Contraindications and precautions in label
- Communication plan, and post-marketing surveillance

Proposed Label: Contraindications

- Habitual or psychogenic polydipsia
- Hyponatremia, history of hyponatremia
- Moderate to severe renal impairment (eGFR <60 mL/min)
- History of known or suspected cardiac insufficiency or other edema forming diseases
- Known or suspected SIADH

Proposed Label: Warnings and Precautions

- In addition to baseline sodium monitoring, additional monitoring of patients ≥ 65 and adults of all ages at risk
- Use caution for concomitant use with drugs associated with causing hyponatremia (monitor sodium for specified drugs)
- Advise patients to restrict fluid (1 hr before to 8 hrs after NOCDURNA administration)
- Halt NOCDURNA use during acute intercurrent illnesses requiring increased fluid intake

Labeling, Communication, and Post-Marketing Surveillance to Minimize Risk

Label/Package	Sodium monitoring plan as a label recommendation • All patients at baseline – normal sodium • Patients ≥ 65 yrs • Patients at increased risk of hyponatremia
	NOCDURNA initiation packaging availability
Communication	Medication guide and website
	Healthcare professional education program
Post-Marketing Assessment	Post-marketing enhanced safety surveillance of hyponatremia
	Prescription claim database study to monitor risk of severe hyponatremia

NOCDURNA Safety Conclusions

- NOCDURNA: favorable safety profile and well-tolerated at proposed doses
  - 1% subjects experienced severe hyponatremia (≤125 mmol/L)
- Hyponatremia
  - Tends to be asymptomatic
  - Dose-, age-, and gender-dependent
  - Tends to occur early
  - Substantially decreased with lower gender-specific doses
- Extensive global post-marketing experience confirms safety is consistent with AEs observed in clinical trials

Hyponatremia

Joseph G. Verbalis, MD

Professor and Chief of Endocrinology and Metabolism

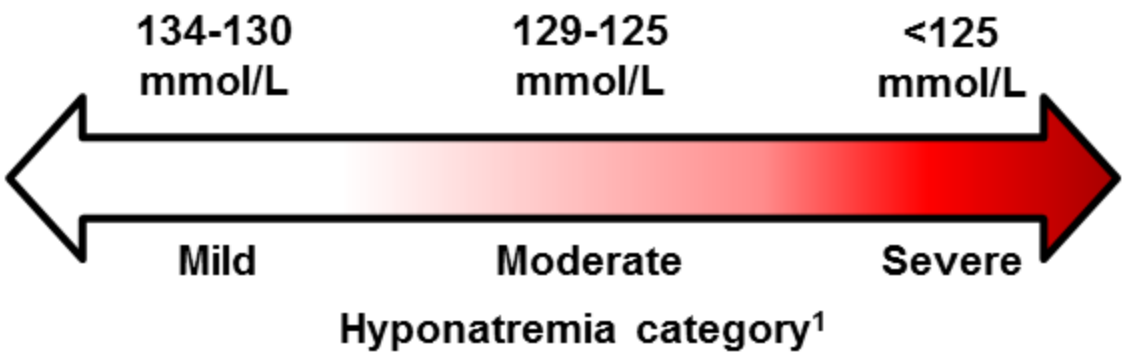
Director, Georgetown-Howard Universities Center for Clinical and Translational Science

Georgetown University

What is Hyponatremia?

- Decreased serum sodium concentration
- Major cause is dilution from vasopressin-mediated water retention[1]

Serum Sodium Lab Values



Potential Symptoms[1]

- Headache
- Irritability
- Nausea
- Mental slowing
- Gait instability
- Falls
- Confusion
- Disorientation
- Delirium
- Seizures
- Stupor
- Coma
- Respiratory arrest

1. Verbalis J et al. *Am J Med* 2013

Prevalence of Hyponatremia in the General Population

- Overall prevalence in the general population low: <2%[1,2]
- Increased prevalences seen with:
  - Increased age (≥ 65): 5-7%[3,4]
  - Hospitalization: 15-30%[2]
  - Disease states (CHF, cirrhosis, COPD)
  - Medications

1. Upadhyay A et al. *Am J Med*, 2006
2. Hawkins, RC. *Clin Chim Acta* 2003
3. Caird et al, *Brit Heart J* 1973
4. Cowen L et al. *Endocrinol Metab Clinic NA*, 2013

Which Drugs are Associated with Increased Risk of Hyponatremia?

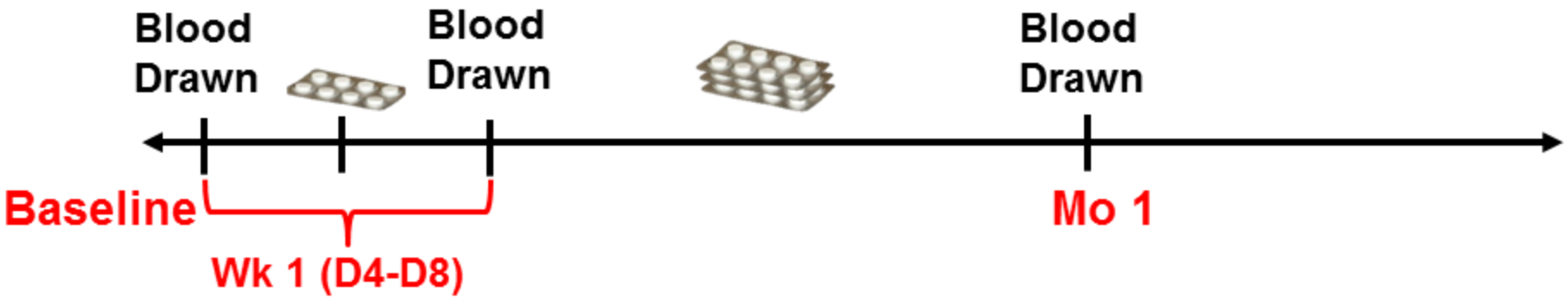
- Many drugs (>50) have been associated with the production of hyponatremia[1]
- The most common are:
  - SSRIs: 0.5-32% hyponatremia incidence[2]
  - Thiazide diuretics: 11-30% hyponatremia incidence[3]
  - Anti-epileptic drugs, carbamazepine: 4.8-40%[4]

1. Verbalis, Diseases of the Kideney, Brenner & Rector, 2014
2. Leung AA et al. *Am J Med*, 2011
3. Jacob S et al. *Ann Pharmacother*, 2006
4. Van Amelsvoort T et al. *Epilepsia*, 1994

Risk of Hyponatremia with NOCDURNA

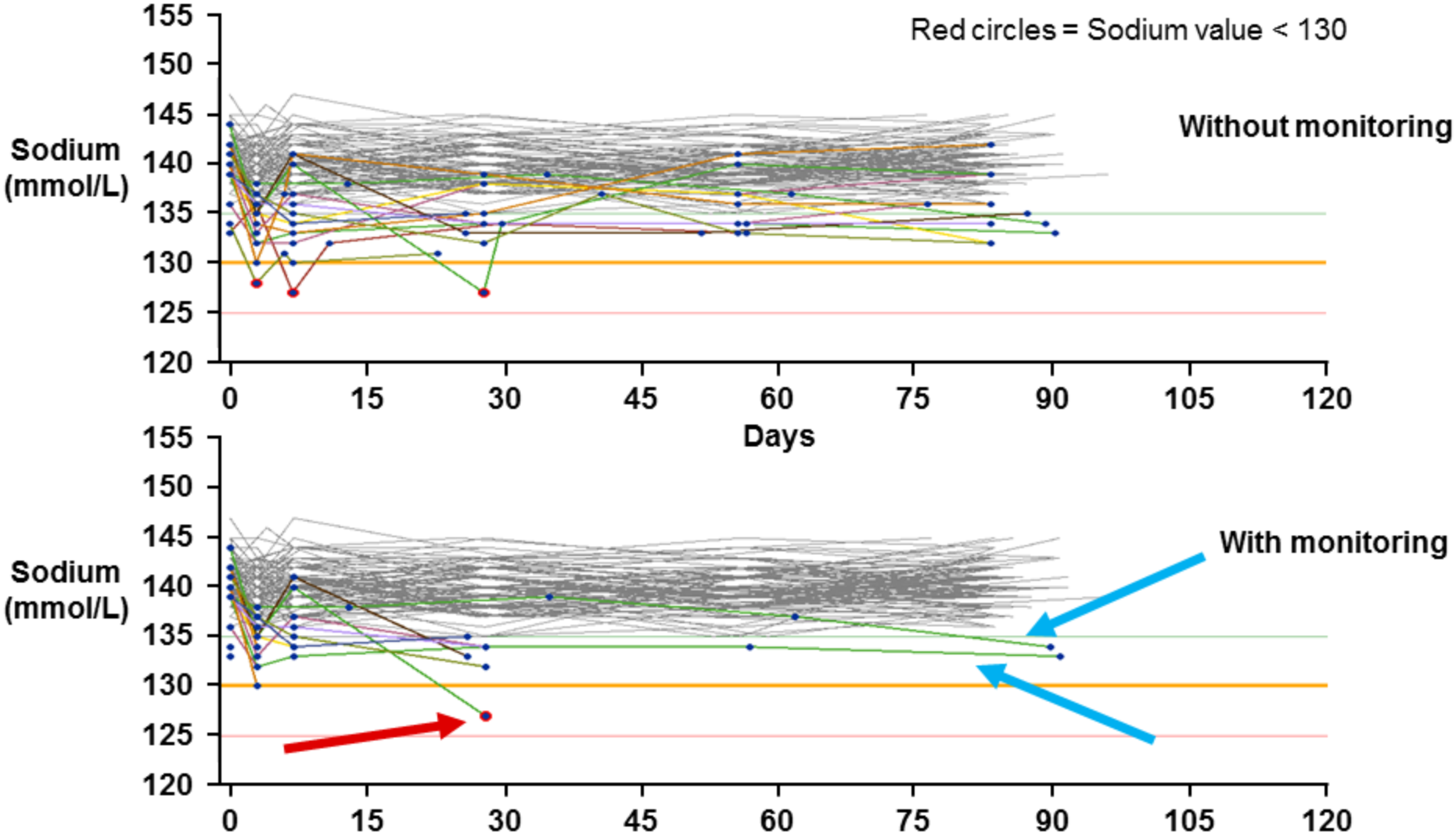
- Incidence of clinically significant hyponatremia in NOCDURNA trials in same range or lower than other commonly used drugs
- No guidelines on acceptable levels of hyponatremia or hyponatremia symptoms
- No currently approved drugs require or recommend hyponatremia monitoring plans
- NOCDURNA: proposed monitoring plan would be the first

Proposed Monitoring Plan for Label to Further Reduce Hyponatremia

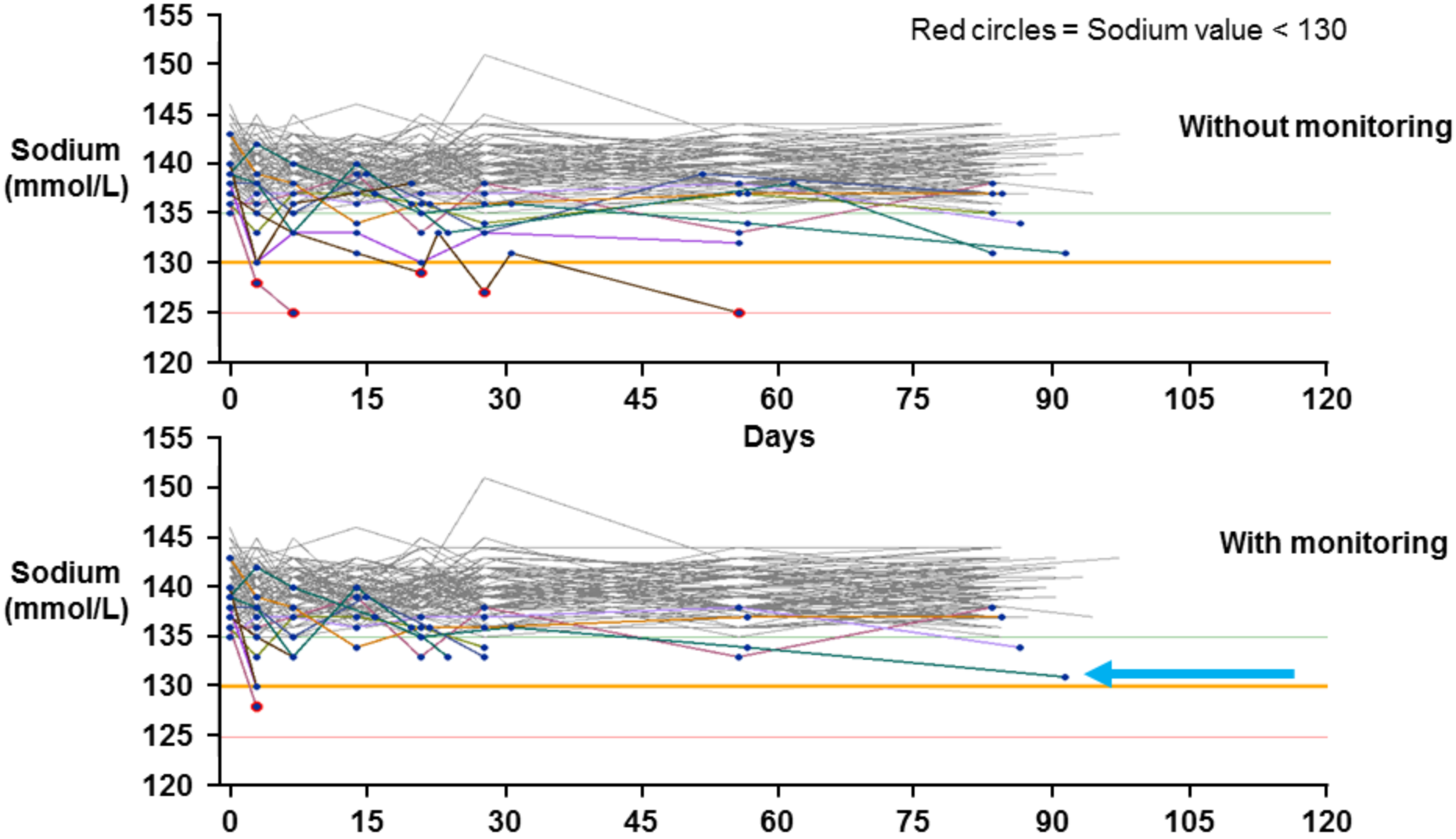


- **Baseline** – **ALL** patients should have normal sodium before starting NOCDURNA
- **Week 1 (4-8 days after initiated treatment) –** following initiation pack for patients at increased risk of hyponatremia (≥ 65 years, on concomitant medications associated with hyponatremia: e.g., SSRI, thiazide, antiepileptics)
- **Month 1 –** following additional prescription for patients at increased risk
- **Sodium <135 mmol/L at ANY time → discontinue treatment**

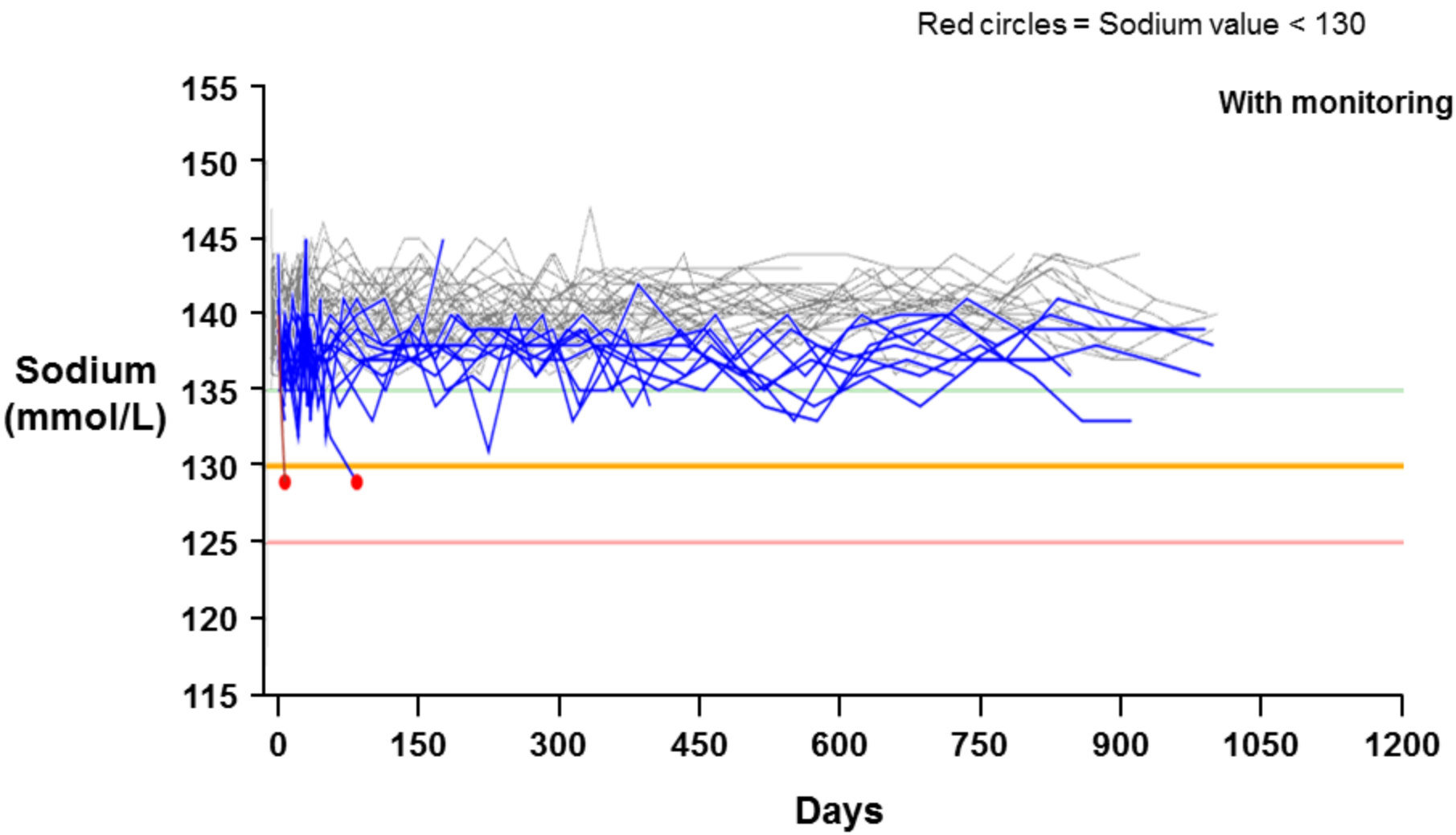
Proposed Monitoring Plan Reduces Risk of Clinically Significant Hyponatremia: CS40 (Women)



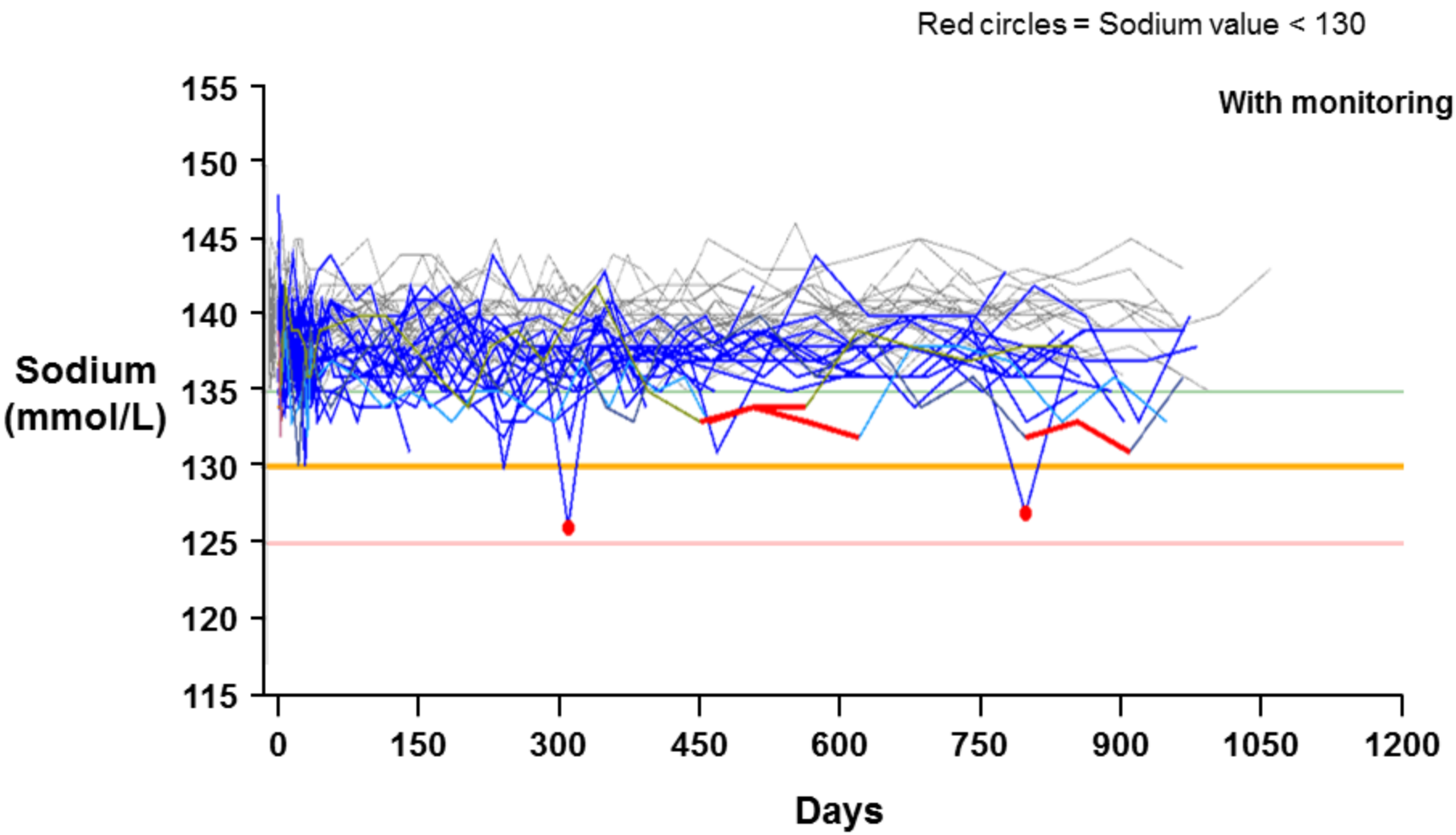
Proposed Monitoring Plan Reduces Risk of Clinically Significant Hyponatremia: CS41 (Men)



Long-Term Serum Sodium Levels with Monitoring Plan Applied in Women (CS29/31)



Long-Term Serum Sodium Levels with Monitoring Plan Applied in Men (CS29/31)



Suitability of NOCDURNA Use in Patients ≥ 65 Years of Age

- NODURNA does not need to be restricted to patients <65 yrs
- Low rate of moderate/severe hyponatremia in elderly
- All severe and virtually all moderate hyponatremia would be eliminated by monitoring plan
  - Subjects eliminated from treatment

Appropriateness of Proposed Serum Sodium Monitoring Plan

- Proposed monitoring plan is optimal
- Longer-term monitoring will not detect clinically significant hyponatremia
  - Should be used with at risk patients
- Trial monitoring time points: Day 7 and Day 30
  - Most hyponatremia occurs in first month of treatment
- Only 4 subjects developed symptoms possibly related to hyponatremia before Day 4
  - Consistent with mode of action of desmopressin

Management of Subjects with Markedly Decreased Serum Sodium (<130 mmol/L)

- Serum sodium ≤130 mmol/L: 12 subjects (8%) instructed to return for repeated serum sodium measurement
  - 11 returned within 16 days (median)
    - 10 of the 11 increased serum sodium to ≥130 mmol/L by next repeat level
    - 1 of the 11, serum sodium increased to ≥130 mmol/L by second repeat (14 days)

Management of Subjects with Markedly Decreased Serum Sodium (<130 mmol/L)

- 3 men had multiple markedly abnormal decreased serum sodium values <130 mmol/L
  - 2 had 2 occurrences
  - 1 had 5 occurrences
- 2 of the 3 would have been captured by monitoring plan
- Subjects with serum sodium values ≤125 mmol/L stopped treatment immediately
- 7 chronic hyponatremia cases (<135 mmol/L for ≥ 3 months)
- With proposed monitoring plan
  - 3 cases of MILD chronic hyponatremia remained
  - No cases persisted

Hyponatremia Summary

- Recognized and well-understood risk
- Unique steps taken to reduce incidence:
  - Dosages reduced to minimum effective doses
  - Gender-specific dosing
  - Sodium monitoring plan
- Sodium monitoring plan results:
  - Only mild, non-clinically significant hyponatremia
  - Within ranges of other drugs associated with hyponatremia

Benefit Risk/Conclusion

Eric Rovner, MD

Professor of Urology

Department of Urology

Medical University of South Carolina

Treatment of Nocturia due to Nocturnal Polyuria is Important

- NP is a major underlying cause of nocturia
- Nocturia due to NP affects sleep, daytime functioning, physical and mental well-being
- Undertreated, mistreated or treated off-label
- No FDA-approved therapies for nocturia due to NP

FDA Briefing Book: New Trial for More Homogeneous and Severe NP Population

- Unlikely to provide additional value
  - Previously studied in NOCTUPUS
  - NOCDURNA trials inclusion/exclusion criteria achieved ~90% NP population
  - Many patients with OAB/BPH have nocturia likely due to NP and would benefit from antidiuretic treatment
  - Pivotal study population consistent with current medical practice

Benefit-Risk of NOCDURNA

Desmopressin	Benefits	Managing Risks
40 years of global experience	Decreases # of nighttime voids	Minimizes clinically significant hyponatremia
Lower dose melt formulation	Improves sleep, sleep quality and patient well-being	
Gender-specific dosing	Addresses unmet medical need for patients of all ages	Proposed thorough post-marketing risk minimization plan
Directed at the specific underlying cause: NP	Provides optimal medical treatment option	

NOCDURNA: Summary and Conclusion

- Clear unmet medical need
- Pivotal trial designs/population agreed in SPA
- Met primary and key secondary endpoints across trials
- Totality and consistency of data demonstrate clinical relevance and improvements in sleep and QoL
- Safety has been appropriately addressed
- Favorable benefit-risk profile

NOCDURNA®
Desmopressin Orally Disintegrating Tablet (Melt)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

January 12, 2015

Back-up Slides

Communications plan

Objectives	• To inform physicians on disease condition; appropriate patient selection; risk of hyponatremia; and importance of monitoring serum sodium levels
Execution of Communication Plan	• Email sent within 60 days of product approval, and at 12 and 24 months post approval to HCPs likely to prescribe NOCDURNA: GPs, family practitioners, internists, urologists • Similar e-mail sent at above time points to key professional organizations for distribution to members
Website and Factsheet for Prescribers	• Prescriber educational website • Factsheet distributed to prescribers at initial detailing visits with HCPs after product approval
Website and Medication Guide for Patients	• Patient educational website • Medication guide targeted to patients provided in NOCDURNA packaging

Demographics and Baseline Voiding Parameters by Gender Across Studies

Mean (SD)	Full Analysis Set			
	Women		Men	
	CS29	CS40	CS29	CS41
	N=341	N=261	N=416	N=385
Age (years)	58.1 (13.7)	59.8 (14.2)	65.1 (11.5)	60.6 (13.1)
BMI (kg/m2)	30.5 (7.9)	30.3 (6.9)	28.8 (5.4)	29.2 (5.0)
Nocturnal voids	3.22 (1.12)	2.86 (0.84)	3.34 (1.16)	2.93 (0.85)
Daytime voids	7.68 (2.40)	5.64 (1.27)	7.27 (2.19)	5.68 (1.20)
FUSP (min)	112 (67.5)	145 (57.2)	117 (61.0)	146 (55.5)
NPI (%)	46.8 (12.1)	46.2 (12.7)	48.4 (12.2)	45.4 (12.0)
Nocturnal Volume (mL)	805 (367)	617 (333)	824 (396)	625 (327)

FUSP = First Undisturbed Sleep Period
NPI = Nocturnal polyuria index

NOCDURNA - Exposure Data from Canada

- NOCDURNA approved/launched in Canada
  - 25 µg in females launched August 2014
  - 50 µg in males launched November 2014
- 344 patients-years* of exposure for 25 µg in women
- 323 patients-years* of exposure for 50 µg in men

*30 November 2014

Post-marketing NOCDURNA – Three Cases of Hyponatremia

- Woman treated with 25 µg NOCDURNA was hospitalized for hyponatremia; No other information is available
- Man treated with 25 µg NOCDURNA; serum sodium decreased from 131 mmol/L to 125 one week later; non-serious
- An unknown age/sex patient with 25 µg NOCDURNA; serum sodium decreased from 135 mmol/L to 127; non-serious

Nocturnal Diuresis at Baseline in Both Women (CS40) and Men (CS41)

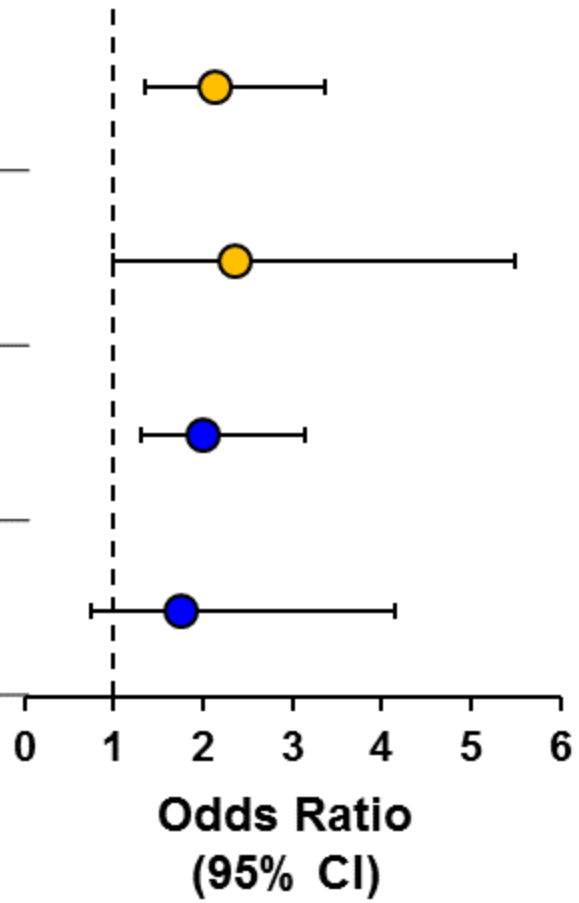
	CS40 (Women)		CS41 (Men)		
	25 µg	Placebo	50 µg	75 µg	Placebo
Urine Volume	N (%)	N (%)	N (%)	N (%)	N (%)
<90 mL/hr	100 (75)	96 (75)	92 (77)	92 (74)	106 (75)
≥ 90 mL/hr	22 (25)	32 (25)	27 (23)	32 (26)	36 (25)

Total NP Population = 25%

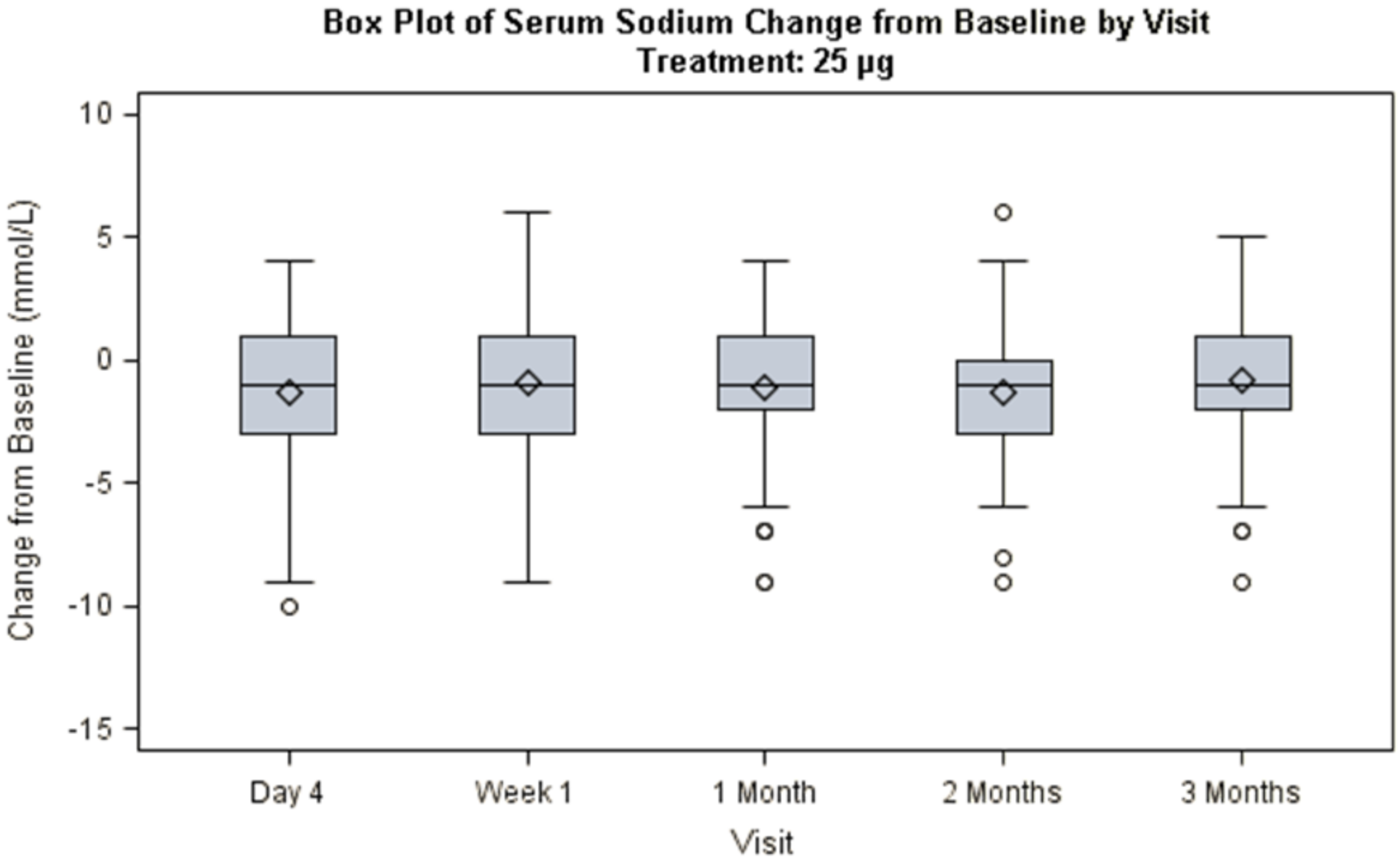
Total NP Population = 25%

Co-Primary 2 Endpoint of 33% Responder Rate in NP Populations

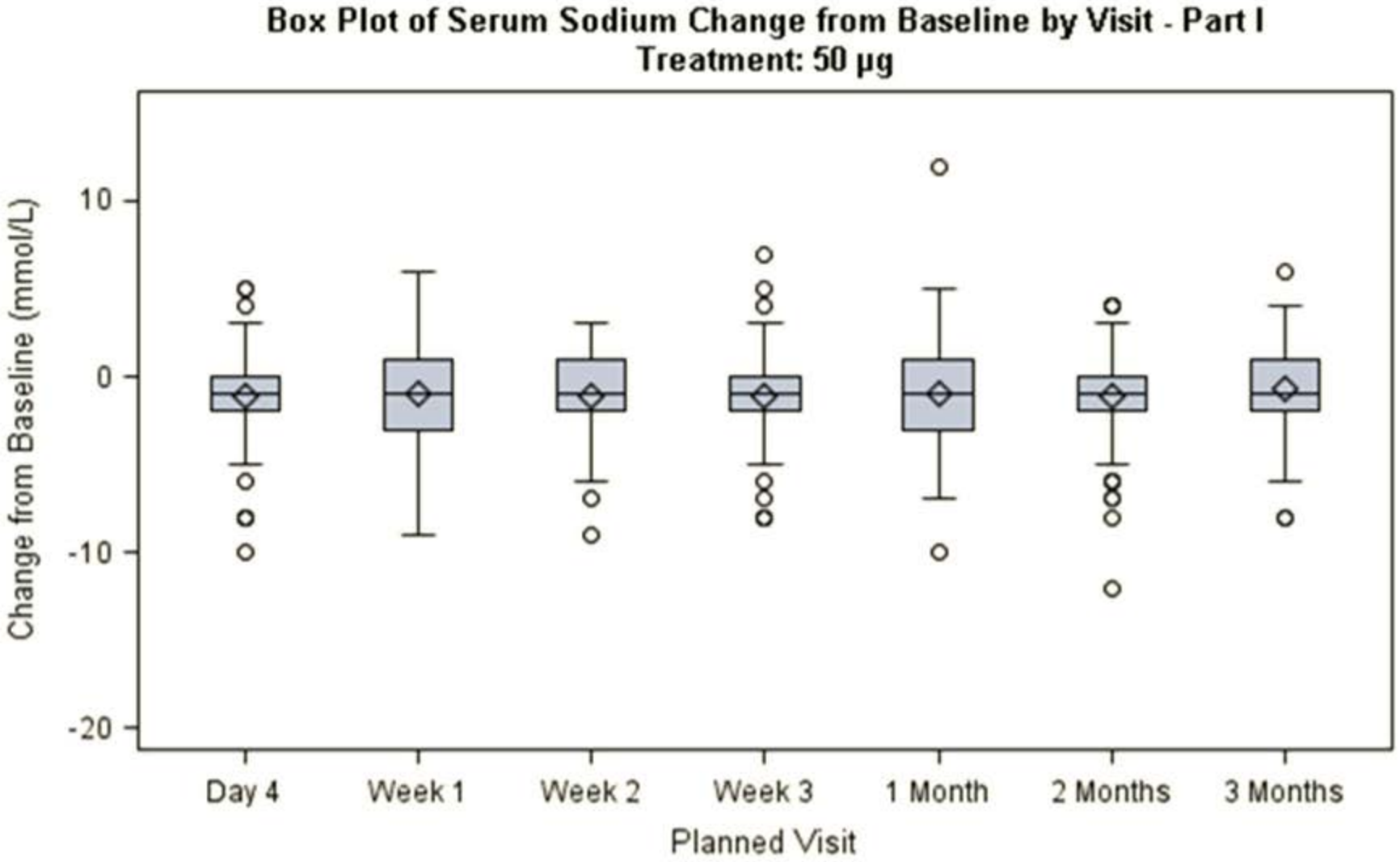
Study	Urine Volume	Placebo N	Placebo Odds	NOCDURNA N	NOCDURNA Odds
Women (CS40)	≥ 33% NPI	111	1.59	114	3.40
	≥ 90 mL/hr	31	1.42	31	3.34
Men (CS41)	≥ 33% NPI	127	1.00	97	2.01
	≥ 90 mL/hr	36	0.85	26	1.49



Change in Serum Sodium Over Time in Female Patients on 25 mcg



Change in Serum Sodium Over Time in Male Patients on 50 mcg



No Efficacy Difference in Patients with Hyponatremia

Serum Sodium Level (Lowest level at any given time point)	N	Δ Mean Change Noct. Voids Co-Primary 1 ≥135:<135	Δ Baseline Noct. Volume ≥135:<135
CS40			
≥ 135 mmol/L	120	-1.45 : -1.60 P=0.515	-242 : -243 P=0.889
<135 mmol/L	13		
CS41			
≥ 135 mmol/L	108	-1.19 : -1.64 p=0.098	-192 : -276 p=0.238
<135 mmol/L	11		

Causes of Placebo Effect

- Placebo effect common in lower urinary tract symptom trials with up to 64%[1] reduction from baseline
- Several factors may contribute
  - Clinical trial setting
    - Lifestyle modifications
    - Physician-patient interaction
  - Regression to the Mean due to inclusion criteria
  - Effect of taking a tablet

Ref: 1. van Leeuwen JH, 2006 (urge incontinence episodes)

Regression to the Mean (RTM) Effect: 32% in Women (CS40) and 45% in Men (CS41) of Placebo Effect

Population Mean # Nocturnal Voids (Screened Population)	RTM Effect * (Mean # Voids Reduction)	RTM Effect as % of Total Placebo Effect	
		Women (CS40)	Men (CS41)
2.0	0.33	27%	38%
2.5	0.40	32%	45%
2.9	0.51	41%	58%

- Total placebo effect over 3 months:
  - 1.24 mean # voids reduction – Women (CS40)
  - 0.88 mean # voids reduction – Men (CS41)

* Estimation using Barnett et al (2004) utilizing data from women (CS40) and men (CS41) placebo arm (Month 2 and 3).

Falls and Fractures Reported in Women (CS40) and Men (CS41)

MedDRA Preferred Term	CS40 (Women)		CS41 (Men)		
	25µg N=135 N (%)	Placebo N=126 N (%)	50µg N=119 N (%)	75µg N=122 N (%)	Placebo N=143 N (%)
Falls	0	1 (<1)	0	1 (<1)	1 (<1)

MedDRA Preferred Term	CS40 (Women)		CS41 (Men)		
	25µg N=135 N (%)	Placebo N=126 N (%)	50µg N=119 N (%)	75µg N=122 N (%)	Placebo N=143 N (%)
Ankle Fracture	1 (<1)	0	0	0	0
Wrist Fracture	0	1 (<1)	0	0	0

All Serum Sodium Normal

Nocturnal Voids Increased in Treatment Free Phase Despite Lifestyle Modifications